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JUNE, 1939

# THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

Official Organ for

THE AMERICAN ACADEMY OF PEDIATRICS

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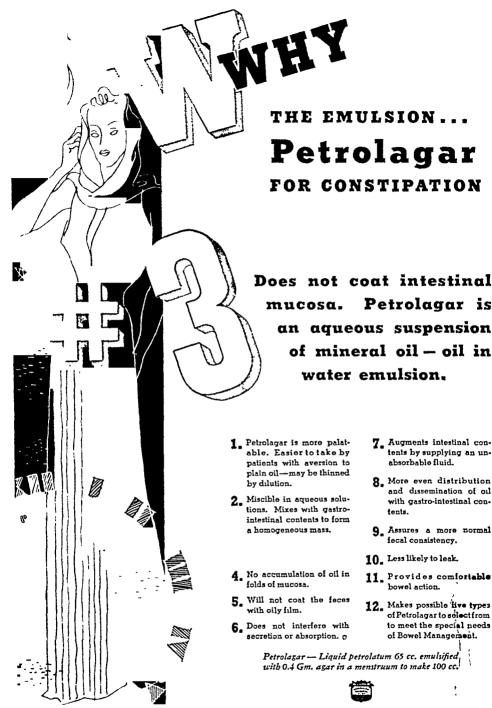
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#### AT NO INCREASED COST TO THE PATIENT

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Vitamin B, potency increased from 25 to 50 International units per gram. Vitamin G (riboflavin) potency increased from 42 to 50 Sherman units per gram. Each tablet now supplies approximately 20 units each of these vitamins, so that dosage may be calculated readily in round numbers by the physician. Supplied in bottles containing 250 and 1,000 6-grain tablets.

#### MEAD'S BREWERS YEAST POWDER

is also thus increased in potency per gram. In addition, it is now improved in texture so that it mixes more readily with various vehicles the physician may specify in infant feeding. Supplied in bottles containing 6 ozs.

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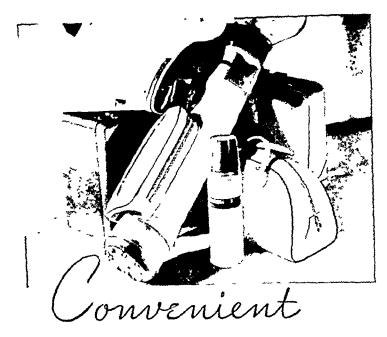
In the field of research, observation and correlation are important elements, and are dependent to a large extent on facilities, modern equipment, and trained personnel.

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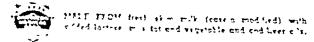


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The mother has only to measure out and place in dry, sterile feeding bottles, the prescribed number of measurefuls of Similac powder for each individual feeding. The bottles containing the measured Similac powder are then capped, and can be conveniently carried, along with a thermos bottle of boiled water cooled to about blood heat. At feeding time it is necessary only to pour into one of the bottles containing the measured Similac powder, the prescribed amount of water, then shake until the Similac is dissolved, place a nipple on the bottle, and feed.



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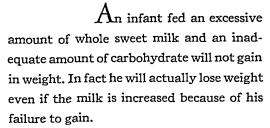
## Why is

## carbohydrate Indispensable in the Infant Formula?



Answers to Physicians' Questions

- Q. What is the minimal carbohydrate requirement in infancy?
   A. About 3 grams per kilo-
- gram of body weight.2. Q. What is the optimal carbohydrate requirement in infancy?
  - A. About 12 grams per kilogram of body weight.
- 3. Q. What amount of carbohydrate does the breast fed infant receive?
  - A. About 12 grams per kilogram of body weight.
- 4. Q. What is the weight of 1 oz. of Karo by volume?
  - A. 40 grams yielding 120 calories.
- Q. What is the caloric value of 1 oz. of Karo by weight?
   A. 28 grams yielding 90 calories.



Some form of carbohydrate must be added to milk to furnish the necessary additional energy. Carbohydrates aid in the absorption of soaps and minerals and help to shift the intestinal reaction toward the acid side.

Clinical experience indicates that a mixed sugar such as Karo Syrup is a most suitable form of carbohydrate for milk modification. Karo Syrup contains a large proportion of dextrin with relatively small amounts of maltose, dextrose and cane sugar.

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Infant feeding practice is primarily the concern of the physician; therefore, Karo for infant feeding is advertised to the Medical Profession exclusively. For further information, write Corn Products Sales Company, Dept. P-6, 17 Battery Place, New York City, N. Y.



Potent but pleasant is White's Cod Liver Oil Concentrate, providing the vitamins A and D of time-proved cod liver oil, in a tablet, a capsule or a drop. With all its potency, White's Cod Liver Oil Concentrate is easy and agreeable to take, free from excess heavy oil and repelling odor.

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#### LIQUID ...

For drop dosage to infants. Two drops provide the vitamin A and D equivalent of not less than one teaspoonful of cod liver oil.\*

#### TABLETS ...

For youngsters and adults, Each pleasant-tasting tablet provides the vitamin A and D equivalent of not less than one teaspoonful of cod liver oil.\*

#### CAPSULES ...

For larger dosage. Each capsule provides the vitamin A and D equivalent of not less than D<sub>2</sub> teaspoonfuls of cod liver oil.\* Ethically promoted, White Laboratories, Inc., Newark, N. J.

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#### COD LIVER OIL CONCENTRATE





## Why is

## carbohydrate Indispensable in the Infant Formula?

INFANT FEEDING PRACTICE POINTERS

Answers to
Physicians' Questions

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   A. 28 grams yielding 90 cal-

An infant fed an excessive amount of whole sweet milk and an inadequate amount of carbohydrate will not gain in weight. In fact he will actually lose weight even if the milk is increased because of his failure to gain.

Some form of carbohydrate must be added to milk to furnish the necessary additional energy. Carbohydrates aid in the absorption of soaps and minerals and help to shift the intestinal reaction toward the acid side.

Clinical experience indicates that a mixed sugar such as Karo Syrup is a most suitable form of carbohydrate for milk modification. Karo Syrup contains a large proportion of dextrin with relatively small amounts of maltose, dextrose and cane sugar.

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Potent but pleasant is White's Cod Liver Oil Concentrate, providing the vitamins A and D of time-proved cod liver oil, in a tablet, a capsule or a drop. With all its potency. White's Cod Liver Oil Concentrate is easy and agreeable to take, free from excess heavy oil and repelling odor.

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For young-ters and adults, Each pleasant-tasting tablet provides the vitamin A and D equivalent of not less than one teaspoonful of cod liver oil.\*

#### CAPSULES ...

For larger dosige, Each capsule provides the vitamin A and D equivalent of not less than W<sub>2</sub> teaspoonfuls of cod liver oil.\* Pthically promoted, White Laboratories, Inc., Newark, N. J. 31, S. P. Minimum Standards.

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### PROPADRINE HYDROCHLORIDE

in the symptomatic relief of hay fever patients

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PROPADRINE HYDROCHLORIDE is a bronchodilator and local vaso-constrictor, with pharmacological properties similar to ephedrine. Its clinical superiority has been emphasized by independent investigators in these statements:



CAPSULES: 36 grain—bottles of 25, 100 and 500; 34 grain—bottles of 25 and 100. SOLUTION: 1% (isotonic)—1-ounce and pint bottles; 3%—1-ounce and pint bottles. (For topical application as a vasoconstrictor in reducing congestion of nasal mucous membranes.)

NASAL JELLY: in 1/2-ounce tubes containing 0.66% Propadrine Hydrochloride.

- I. Propadrine Hydrochloride may be administered in therapeutic doses with relative freedom from nervousness or insomnia.
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- **3.** Propadrine Hydrochloride has proved a very satisfactory and valuable therapeutic agent in the treatment of allergic manifestations.
- 4. While the relief obtained from a single dose is equal to that produced by ephedrine, the absence of nervousness and insomnia makes it possible to use propadrine at frequent regular intervals and obviates the necessity of combining with it a sedative. Used in this manner, the results are definitely better than can be obtained by the usual irregular use of ephedrine.
- 5. The use of propadrine every three or four hours gave more relief to the patients suffering with urticaria and angio-neurotic edema than any other medication these investigators found.
- **6.** In children, Propadrine Hydrochloride is not likely to produce restlessness or walking or talking in their sleep.

Propadrine Hydrochloride (phenylpropanol-amine hydrochloride) is supplied as indicated under the illustration.



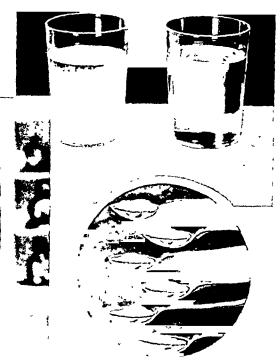
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## An A-B-C of Alpha and Beta Lactose

A. Five Times More Soluble—that's one advantage of Beta Lactose, Borden, over ordinary milk sugar (alpha lactose). That's why patients find it easier to use.



B. More Palatable, too-that's what your patients' verdict is when switched to Beta Lactose, Borden. They're pleased to find it so much cases to the.

C. Particularly Helpful—that's what you'll find Beta Lactose, Borden, in adult intestinal therapy, or in the preparation of infant-feeding formulas. It is a milk sugar of choice.

	Bos	deris	
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	and another property as	-		M D.
×19.,+	* ***			

#### Diarrhea in Infancy

### Take It In Time

Just a day or two of light nourishment prepared from Mellin's Food as suggested below will usually avert an intestinal disturbance that might develop into a serious diarrhea if not taken in hand at the first appearance of loose stools.

Mellin's Food\*. . 4 level tablespoonfuls Water (boiled, then cooled) . . . 16 ounces

Give one to three ounces every hour or two until the stools lessen in number and improve in character.

The mixture may then be strengthened by the gradual substitution of boiled skimmed milk for water until the quantity of skimmed milk is equal to the normal quantity of milk used in the baby's formula. Finally the fat of the milk may be gradually replaced by skimming less and less cream from the milk.

Samples sent to physicians upon request.

Directions for using Mellin's Food are left entirely to the physician.

Mellin's Food Company, Boston, Mass.

### SULFANILAMIDE

is easier
to administer
to infants and
children in this
safe and effective

### ORAL SOLUTION





Each ounce of 5 Minute Cream of Wheat provides 12 mg. iron which, as shown by extensive clinical studies, prevents nutritional anemia of the infant if an average amount of the cereal is fed daily.

#### CALCIUM

New 5 Minute Cream of Wheat contains 143 mg. calcium and 168 mg. phosphorus per ounce. thus contributes measurably toward satisfying the daily requirements of these essential minerals.

#### VITAMIN

Through the addition of wheat germ (stabilized to prevent rancidity). each ounce of the New 5 Minute Cream of Wheat is enriched with 15.5 international units of vitamin B1. It is thus on excellent source of this vitamin for infants.

#### RICH IN AVAILABLE PHOSPHORUS. CALCIUM, IRON, VITAMIN B.

Through the addition of stabilized wheat germ, tricalcium phosphate, disodium phosphate, and ferric orthophosphate, Cream of Wheat now provides, in readily assimilable form, minerals essential for proper growth and development. The former desirable qualities of Cream of Wheat remain unchanged; the new preparation has a richer, wheatier flavor, cooks to a deeper, creamier color.

#### AN IDEAL FIRST SOLID FOOD

New 5 Minute Cream of Wheat is now more than ever advantageously employed as a first solid food for infants. In addition to its rich store of nutritive elements, it supplies iron which is usually deficient in the infant's dietary, and complements the calcium and phosphorus contained in milk, thus adequately satisfying the daily requirements of these minerals.

#### AN EXCELLENT CEREAL FOR EVERY AGE

Because of its appealing taste and many nutritional advantages, New 5 Minute Cream of Wheat finds an important place in the dietaries of young and old alike. It cooks to thorough digestibility in 5 minutes of boiling, thus is easily prepared and economical to use, especially since its price is the same reasonable figure at which Cream of Wheat has always been offered.

#### CREAM THE 0 F WHEAT CORPORATION MINNEAPOLIS, MINN., U.S.A. The Cream of Wheat Corporation. Minneapolis, Minn. Gentlemen: You may send me a 14 oz. trade package of Cream of Wheat, together with literature. Dr.\_\_\_\_ Address ... City and State \_\_\_\_ JP 6-39



## WEIGHT LOSS following TONSILLECTOMY?

After tonsillectomics there is generally a weight loss. Sometimes this loss may be extreme enough to cause complications. The physician, anxious to prevent weight decrease, now has an excellent

feeding regime at his command.

Stovin\* reports excellent results with a group of tonsillectomy patients. COCOMALT was given in cold milk four hours after the operation and continued regularly thereafter.

"Nutrition Studies Following Tonsillectomics"— Stovin, J. S., Medical Record—149:63, 1939.

RESULTS: 36% gained weight, while 22% retained their original weight. COCOMALT was gentle to the recently traumatized tissues and minimized post-operative irritability. Decrease in post-operative complaints at the end of the week was marked.

cocomalT makes a delicious, economical malted food drink, rich in calcium, phosphorus, iron, and Vitamins A and D. Its delightful palatibility encourages children to drink milk readily.

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- Milk Sugar is the only sugar found in mother's milk.
- Milk and solutions of Milk Sugar contain an equilibrium mixture of approximately two parts of alpha lactose and three parts of beta lactose.
- In solution, both alpha lactose and beta lactose are converted to an equilibrium mixture similar to that found in milk. This conversion is virtually instantaneous at 70°C.
- Irrespective of whether alpha lactose or beta lactose is used for the modification of cow's milk in infant feeding, the modified preparation will contain the same equilibrium mixture of two parts of alpha lactose and three parts of beta lactose.

LITERATURE ON REQUEST

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(Lactose U S P )

An Eminently Safe and Satisfactory Carbohydrate for Infant Feeding.



MERCK & CO. Inc. Manufacturing Chemists RAHWAY, N. J.

#### Aiding the Come-back from Diarrhea...



To INFANTS whose digestive capacity and strength have been sapped by diarrhea, DRYCO can bring help of vital value.

To rebuild depleted tissues, DRYCO modifications provide ample protein.

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To assure tolerance, particularly by very young or markedly asthenic infants, DRYCO is more readily digestible.

DRYCO'S readier digestibility permits a return to the full maintenance ration more rapidly than is usually possible with commonly used fluid milk formulas.







#### LIFE AND LETTERS OF DR. WILLIAM BEAUMONT

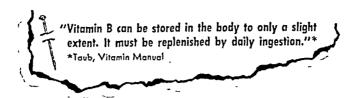
By JESSE S. MYER, A.B., M.D.

Introduction by SIR WILLIAM OSLER, Bt., M.D., F.R.S.

Tills is a reprint of the original book published in 1912, with corrections and some new text and illustrations added. During recent years more and more interest is being manifested by physicians and others in the life of Dr. Wm. Beaumont and his remarkable experiments on the physiology of digestion, and also the subject of his experiments. Mexis St. Martin. The book is beautifully printed, handsomely bound with a special jacket in colors, and a two-page color insert of an original painting by Cernwell. It is really a DeLuxe Edition that you want to have in your library.

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#### How daily servings of RALSTON WHEAT CEREAL protect against Vitamin B<sub>1</sub> deficiency

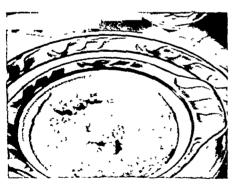


DOCTORS AGREE that infant diets must be strictly regulated. Unregulated diets often result in Vitamin Bi deficiency, since each infant requires 50 International Units daily.\* The diet prescribed must replenish this, Units daily.\* The diet presented mast represent day by day, to protect against deficiency.

\*U. S. Dept. of Agriculture, Missellaneous Pub. No. 275, page 22.



ADULTS AND ADOLESCENTS normally require 200 International Units of Vitamin Bidaily. "However, since most children, and many adults, ingest an abnormal amount of carbohydrates, their daily requirement is much higher. This is not available in American diets, which may contain little more than the minimum required to protect against actual deficiency.



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added to most diets, protects against Vitamin By deficiency. Made from whole wheat, with only the coarsest bran removed, it is enriched with wheat germ, which contains 7 times as much Vitamin B1 as whole cereal or eggs... 16 times as much as spinach...40 times as much as milk. It supplies, in one serting, about 1/2 of the infant, and 1/4 of the adult and adolescent daily requirement, Ralston also contains abundant energy producing elements. wheat proteins, minerals and carbohydrates.

Ralston cooks in 5 minutes - costs less than 16 a serving. Delicious in flavor, it is THE hot wheat cereal children really like to eat.

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Address (This offer limited to residents of United States)



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#### Clapp's Strained Foods...

-finely strained, but not too liquid, offer correct texture for the tiny baby in hot weather.



Priscilla Skewis at 3 months



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-avert second-summer upsets by wide variety of coarser foods, uniformly chopped,



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THE attractive Clapp diet, planned for babies and young children, reduces the temptation on mother's part to give baby tastes of adult food.

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#### Clapp's Program of Graded Infant Feeding

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Junior Dinners-Beef with Vegetables . I amb with Vegetalles . I iver with Vegetables

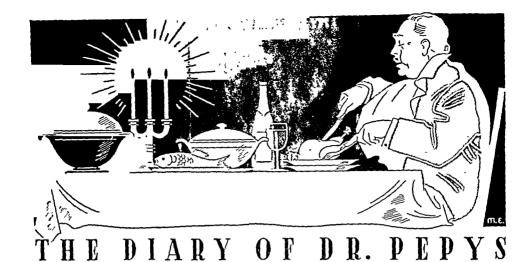
Vegetables-Carro's . Spinach . Beets . Green Beans Mixed Greens

Fruits-Aprile Sauce . Prunes



## © CLAPP'S BABY FOODS

STRAINED FOR BABIES .... CHOPPED FOR YOUNG CHILDREN



Up betimes and to the office, there to find before me the Banker Castlemaine who, at the instant of my entrance, declareth himself distressed.

A pompous gentleman, much given to publick dining. He hath for three nights sat late at banqueting, which he will never forego.

I did prescribe Cal-Bis-Ma for him for the quick relief he finds in this fine powder.

.... Dr. Pepys is right. When hyperacidity gives rise to gastric distress, Cal-Bis-Ma will give prompt and prolonged relief. Sodium bicarbonate and magnesium carbonate for quick action; calcium carbonate and bismuth for prolonged effect, and colloidal kaolin to adsorb the gas formed in the neutralization process. These ingredients, carefully matched for density, are held together in a colloid base that assures uniform distribution and dosage. Trial supply gladly sent to physicians.

## CAL-BIS-MA

A WILLIAM R. WARNER PRODUCT for gastric neutralization and sedation

Powder in tine of 12, 4 and 16 ounces; tablels in boxes of 30, boltles of 110

WILLIAM R. WARNER & CO., INC., 113 West 18th Street, New York City



## A RECOGNIZED INDICATION FOR VITAMIN B

THE numerous indications for vitamin  $B_1$  are readily met with Betaxin which is now available in a distinctively palatable form, the Elixir, and in tablets and ampules of various dosages as well as in vials. Treatment, prophylactic or therapeutic, can be conveniently carried out in patients of all ages for the various conditions in which the lack of vitamin  $B_1$  is the evident or very likely cause for the symptoms.

Betaxin is an active physiologic principle of definite chemical composition and specific effect. It differs from the vitamin B preparations so widely exploited to the public, most of which contain only a minute amount of vitamin  $B_1$ .

HOW SUPPLIED: Tablets of 0.1 mg., 0.5 mg., and 1 mg., bottles of 50; tablets of 5 mg., bottles of 25, 100 and 500. Hypodermic tablets of 6 mg., tubes of 20.

Elixir of palatable wine base, containing 5 mg. in each fluidounce (0.625 mg. per teaspoonful), alcohol 9%, benzoic acid 0.1%, bottles of 8 fluidounces and 1 gallon.

Ampules of 1 mg. (1 cc.), boxes of 10 and 100; ampules of 10 mg. (1 cc.), boxes of 5 and 25; vials of 100 mg. (10 cc.) and 250 mg. (10 cc.).

Each 1 mg. of Betaxin is equivalent to 333 international units of vitamin  $B_1$ . As Betaxin is crystalline vitamin  $B_1$  hydrochloride in pure form, it is not and can not be excelled in potency by any vitamin  $B_1$  preparation of synthetic or natural origin.

Literature and sample on request



Reg. U. S. Pat. Off. & Canada

Brand of THIAMIN CHLORIDE

ELIXIR TABLETS AMPULES

VIALS

First Synthetic Crystalline Vitamin B<sub>1</sub> Hydrochloride

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## Consider The Extra Quality Of HEINZ STRAINED FOODS!



YOUR confidence in the outstanding superiority of Heinz Strained Foods is supported by reliable assurances of their extra quality. When you recommend Heinz, you know that the infants and softdiet cases in your care are getting plus value—for these reasons:

First—Heinz conscientiously selects only the choicest fruits, vegetables, meats and cereals available—cooks and packs them scientifically to insure the maximum retention of vital nutrient factors.

Second – Every tin is enamel-lined to protect savory flavors and appetizing colors – and every tin is stamped with the date of manufacture.

Third—All Heinz Strained Foods on dealers' shelves after a limited period are replaced by fresh products. Furthermore, you'll find that even your very youngest patients enjoy the delicious taste of all 12 kinds!

Heinz Strained Foods bear the Seal of Acceptance of the American Medical Association's Council on Foods—and the Heinz 57 Seal, a symbol of purity and flavor for 70 years!





## HEINZ STRAINED FOODS

12 KINDS—1, Vegetable Soup. 2. Peas 3. Prunes. 4. Tomatoes. 5. Green Beans, 6. Spinach. 7. Apricots and Apple Sauce 8. Mixed Greens 9 Beets. 10. Beef and Liver Soup. 11. Carrots. 12. Cereal.

# Everything but the SPHYGMOMETER"



A VISITING physician, observing the elaborate system of scientific tests employed in a Carnation Milk evaporating plant, remarked: "You seem to have everything but the sphygmometer!"... This appreciative jest emphasizes the extreme

care practised in all Carnation plants. An exacting routine rejects milk for excess acidity, sediment, or "off" odor. It insures uniformity in composition and vitamin

D potency. It guarantees complete sterilization—for ready digestibility and perfect safety.... All Irradiated Carnation Milk, regardless of when or where it may be purchased, carries with it this same trustworthy assurance of uniform, dependable quality.

A BOOKLET FOR PHYSICIANS—Write for "Simplified Infant Feeding," an authoritative publication treating of the use of Irradiated Carnation Milk in normal and difficult feeding cases . . . Carnation Company, Milwaukee, Wis.; Seattle, Wash. Carnation Company, Ltd., Toronto, Ontario.

## CARNATION MILK



Cook1, in a report covering 600 patients, showed that, in 90 per cent of cases with uncomplicated bacillary infection of the urinary tract, the urine was rendered sterile by mandelic acid therapy. Newns and Wilson2 reported that in 36 cases of pyelitis in children under 12 years of age, 24 of which were acute, the urine was rendered sterile in all but three instances, generally within a week of the commencement of treatment. Numerous3 other clinical reports are confirmatory.

Mandelic acid therapy is preferable to the ketogenic diet in many ways. It is more consistently effective and simple to use, does not require hospitalization or dietary restrictions, and seldom produces nausea. It may be used in conditions where the diet is contraindicated, such as in gastric or duodenal ulcer, diabetes, arteriosclerosis, and biliary tract disturbances.

#### Tablets Readily Taken

Squibb Mandelic Acid preparations offer a particular advantage in that they are supplied in tablet form exclusively and are therefore more agreeable and pleasant to take than liquid preparations.

Both the calcium and ammonium salts of mandelic acid are available under the Squibb label.

Squibb Offers Three Dosage Forms:

Tablets Ammonium Mandelateuncoated

7 1/2 grains, in bottles of 200 and 1000

334 grains, in bottles of 100 and 500

Tablets Ammonium Mandelateenteric-coated

5 grains, in bottles of 200 and 1000

Tablets Calcium Mandelateuncoated

71/2 grains, in bottles of 200 and ากกกั

To facilitate the control of urmary acidity, Nitrazine Test Paper and color chart are supplied with all bottles. With Nitrazine\*—a sensitive indicator—one may quickly and accurately determine the acidity or alkalinity of the urine.

For literature address the Professional Service Department, 745 Fifth Ave., New York, N. Y.

#### E.R. SQUIBB & SONS, NEW YORK

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

<sup>\* 1</sup> Squibb trade-mark.

Cook, E. N., and Buchtel, H. A.: Proc. Staff. Meet., Mayo Clinic 11:538, Aug. 19, 1936. Newns, G. H., and Wilson, Reginald Lancet 2 1087, Nov. 7, 1936

Rosenheim, Helmholz and Osterberg; Carroll, Lewis and Kappel; Budge; and others.



\* as disposable diapers or bedpads.

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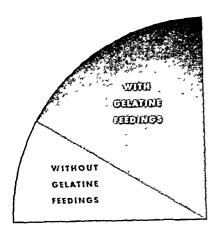
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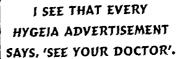
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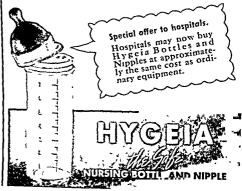




### How a Country Doctor saw his idea carried to millions

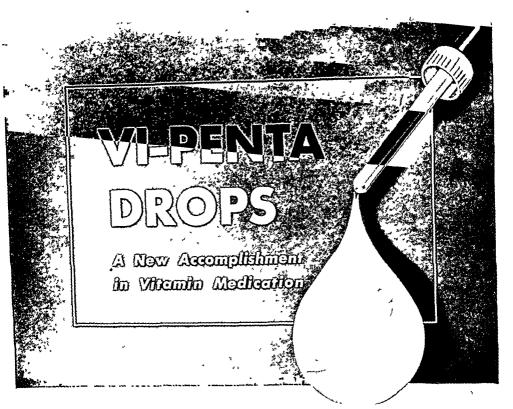
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  - By R. A. Lyon, M.D., and Miner Seymour, M.D., Cincinnati, Ohio,
- CONGENITAL SYPHILIS. II. COMPARISON OF TREATMENT WITH ACETARSONE AND OTHER ARSENICALS.
  - By R. A. Lyon, M.D., and F. C. O'Neil, M.D., Cincinnati, Ohio.
- THE ROLE OF THE PEDIATRICIAN IN MENTAL HYGIENE.
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- THE GASTROINTESTINAL RESPONSE OF CHILDREN TO TEST MEALS OF BARIUM AND PASTEURIZED, EVAPORATED, AND BASE-ENGHANGED MILKS.
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  - By Lydia J. Roberts, Ph.D., Ruth Blair, Gertrude Austin, and Grace Steininger, Chicago, Ill.
- THE SUPPLEMENTARY VALUE OF THE BANANA IN INSTITUTION DIETS, II. CAPILLARY RESISTANCE AND REDUCED ASCORBIC ACID IN THE BLOOD PLASMA.
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  - By John W. Holmes, M.D., J. Albright Jones, M.D., and Nathaniel Gildersleeve, M.D., Philadelphia, Pa.
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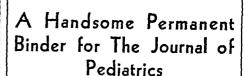
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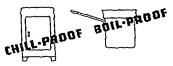
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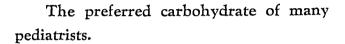
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# The Journal of Pediatrics

Vol. 14 June, 1939 No. 6

## Original Communications

SEPSIS OF THE NEWBORN INFANT
MAURICE L. BLATT, M.D., AND A. ALVIN WOLF, M.D.
CHICAGO, ILL.

HERE has been a sharp drop in the general morbidity and mortality rate in infancy and childhood during the last fifty years. The rate during the first month of life, however, has remained almost stationary; the decrease having occurred in the age brackets above the neonatal According to the U.S. Burcau of the Census for 1935, 32 deaths per 1,000 live births occurred during the first month, in comparison with 23 deaths per 1,000 in the succeeding eleven months of the first year. Of the 32 deaths during the first month, 25 are attributed to natal and prenatal causes. Prematurity, congenital malformations, birth injuries, syphilis, tetanus, and sepsis are among the prominent causes of death in this period. The death rate from prematurity, birth injuries, syphilis, and tetanus has been materially reduced by improvements in technique and prenatal care. Deaths due to congenital malformations are subject to reduction in rate with improvement in surgical technique. There is a minimum, however, in each of these classifications below which reduction is unlikely. The incidence of deaths from sepsis has not been reduced, but on the contrary epidemics, apparently of sepsis, have occurred with increasing frequency in the neonatal group in hospitals previously free from infections. Our efforts, therefore, should be directed particularly toward the control of sepsis in the newborn infant. In the United States nursery infections have occurred from coast to coast, and similar epidemics have been reported from several foreign countries. institutions have had recurrences.

The disease has been ascribed to different microorganisms, by various observers, and, because of the prominence of diarrhea as a symptom, most authors have classified these epidemics as infectious diarrhea. However, a lack of clinical data preceding the onset of the diarrhea in the cases reported makes it difficult for a critical reviewer to differentiate these from epidemics of "sepsis in the newborn in-

695

From Children's Division, Cook County Hospital and the University of Illinois,

fant." The fact that the newborn babies are known to have low resistance to pyogenic organisms and that such invasion is often accompanied by frequent stools makes an assumption of "sepsis" as a primary disease seem more logical than a diagnosis of primary diarrhea. This differentiation is important since control of such epidemics must be based upon a knowledge of the medium through which the infection enters a nursery or is transmitted from infant to infant. Contact, air-borne and food-borne infections are all possible, and each may be accompanied by sepsis manifesting itself by diarrhea.

The atria of infection in the newborn infants are not only the gastrointestinal but also the skin and respiratory tracts. Diarrhea follows primary infections of the gastrointestinal and upper respiratory tracts with equal frequency. It not infrequently follows sepsis with primary infection in the skin, subcutaneous tissue, or umbilical vein.

Several epidemics of "sepsis" have occurred in the newborn infants under our observation. Individual infants in each of these epidemics have had diarrhea, but bronchopneumonia occurred in several and endocarditis in one, without evidence of intestinal irritation.

The clinical histories and laboratory reports of 27 patients seen in an epidemic observed in December, 1937, at Cook County Hospital, are presented. The necropsy reports of the 7 who died are included. The epidemic occurred in the nursery of Ward 51 assigned to normal obstetrics where there were 168 births and in Ward 41 devoted to pregnant women with syphilis, gonorrhea, and acute infections, in which there were 34 live and 5 stillbirths. A contiguous Ward 50 assigned to operative and complicated obstetrics, with 102 live and seven stillbirths, was unaffected.

To recapitulate, twenty-seven infants showed septic symptoms when 277 other newborn infants in the same wards were unaffected.

The clinical picture at the onset of the disease was similar in all cases. Loss of appetite and failure to gain weight were the prominent symptoms. They preceded any change in the number, consistency, and color of the stools by several days. The early loss of weight was not explainable as a result of vomiting or diarrhea. About the third day after onset the stools of some became softer and in some instances, liquid. The color changed to greenish yellow with the occasional presence of mucus. The average number of stools per day was five with the minimum of three and the maximum of eight. No rise of temperature occurred during the first three days, after which a rise to 100° F. occurred in most instances. Several, developing bronchopneumonia, had a higher temperature during this second phase of the disease.

Listlessness was present during the first phase of the disease and continued throughout its entire course. The children seemed to be in no discomfort but had to be urged to take food. Their general appearance seemed to be that of an intoxication rather than of a localized infection.

From the fourth day on the children could be divided into five groups symptomatically:

- A. A group, which following the period of lethargy and weight loss, went on to uneventful recovery without developing respiratory or intestinal symptoms.
- B. A group in which diarrhea was the prominent symptom. All recovered.
- C. A group with stationary or slight increase in weight, mild gastrointestinal disturbance (frequent and soft stools), and gradually disappearing lethargy. These were improved at the end of a week and completely recovered at the end of the second week.
- D. A group with mild bronchopneumonia, temperature rising to 102°-104° F., with recovery at the end of ten to fourteen days.
- E. A group with severe intoxication with or without symptoms of bronchopneumonia or gastrointestinal disturbance. All died.

As the patient improved, lethargy became less, food was taken more readily, stools became less frequent and more normal, temperature approached normal, and a slow steady gain in weight began.

#### CASE HISTORIES

#### Ward 41 (Venereal Disease and Other Infections)

Case 1.—Baby of L. Sc., born Dec. 10, 1937; weight, 2,520 gm.; normal delivery, eight months' gestation; initial feeding, evaporated milk mixture; mother had a doubtful Kahn test. Considerable mucus was present in the infant's pharynx at birth and after its aspiration, an ampoule of alpha lobeline was administered.

Symptoms.—On Dec. 13, 1937, a diffuse erythema with brawny induration and sharply demarcated and elevated borders appeared, involving the left side of the head, face, chin, and shoulder. It was diagnosed erysipelas, and baby was transferred to the Contagious Division. Prontylin therapy was instituted, and the lesion cleared in three days, leaving a localizing abscess of the upper outer third of the left arm.

Course.—Infant transferred to Children's Division, Dec. 16, 1937. On Dec. 17, 1937, liquid stools were first noted, after which there were four to six soft or liquid stools daily.

Laboratory Findings .- Stool cultures yielded B. pyocyaneus.

Diagnosis,-Sepsis.

Result.—Patient expired Dec. 27, 1937.

.iutopsy Findings.—Multiple abscesses of the scalp and left shoulder region; focal bronchopneumonia; cloudy swelling and fatty changes of the liver and kidneys; infectious hyperplasia of the spleen.

Post Mortem Bacteriology.—Aeroine and anaeroine cultures revealed B. coli in the heart blood; B. coli and B. mucosus capsulatus in the colon; B. mucosus capsulatus and B. coli in the ileum.

CASI 2.—Baby of H. E., born Dec. 12, 1937; weight, 2,700 gm.; normal delivery; initial feeding, evaporated milk mixture; mother's Wassermann, positive.

Symptoms.—Persistent loss of weight, slight elevation of temperature (99° F., axillary) and loose stools Dec. 20, 1937.

Course -Transferred to Children's Division Dec. 20, 1937. There were three to four stools daily, some liquid.

Laboratory Findings .- Stool cultures yielded B. pyocyaneus.

Diagnosis - Bronchopneumonia with secondary diarrhea.

Result .-- Patient expired Dec. 23, 1937.

Autopsy Findings.—Focal and confluent bronchopneumonia: parenchymatous degeneration of the liver, kidneys, and myocardium; malnutrition and dehydration; hyperplasia and hyperemia of Peyer's patches.

Post Mortem Bacteriology.—Mixed growth from intestine containing B. pyo cyancus.

CASE 3—Baby of D. W., born Dec. 10, 1937; weight, 3,015 gm.; normal delivery; initial feeding, evaporated milk mixture; mother, two plus Kahn. X-ray reported no evidence of syphilis in infant's long bones

Symptoms —On Dec. 19, 1937, the buttocks were excernated and on Dec. 20, 1937, the child became listless, developed grunting respirations, abdominal distention, and a temperature of 95.4°  $\Gamma$ . rectally.

Course.-Tran-ferred to Children's Division, Dec. 20, 1937.

Laboratory Findings .- No stool cultures.

Diagnosis -Bronchopneumonia.

Result .- Death Dec. 20, 1937-four hours after transfer.

Autopsy Findings — Diffuse bionchopneumonia; infectious hyperplasia of the spleen; passive congestion of the liver, spleen, and kidneys; edema and hyperemia of the brain.

Post Mortem Bacteriology .- No cultures taken.

CASE 4.—Baby of E P., born Dec. 12, 1937, weight, 3,105 gm.; normal delivery; initial feeding, evaporated milk mixture, mother had doubtful Kahn.

Symptoms -Infant sneezed, had sniffles, temperature 101° F. rectally, and a watery stool.

Course -Transferred to the Children's Division Dec. 21, 1937. There were three to seven stools daily, several watery.

Laboratory Findings -- Stool cultures were negative for the colon typhoid, salmonella group, and B. pyocyancus.

Diagnosis - Infection of upper respiratory tract, with secondary diarrhea.

Result .- Discharged cured, Jan. 22, 1938.

CASE 5.—Baby of P II, born Dec. 4, 1937; weight, 2,940 gm.; normal delivery; initial feeding, evaporated milk mixture; mother had a four plus Wassermann; a ray of the infant's long bones was reported negative for syphilis.

Course.—Discharged as normal newborn infant, Dec. 13, 1937. Admitted to Children's Division Dec. 26, 1937.

Sumptoms.—Difficult respirations and sub-equently four to five loose green stools daily.

Laboratory Findings -No cultures done.

Diagnosis - Bronchopneumonia with secondary diarrhea.

Result .- Death ten hours after admission

Autopsy Findings - Catarrhal enterocolitis; focal bronchopneumonia; anemia and parenchymatous degeneration of the myocardium, liver, and kidneys.

Post Mortem Bacteriology.—B. mucosus capsulatus from the heart blood; B. mucosus capsulatus predominating with B. coli and B. proteus in the bile; B. mucosus capsulatus predominating with B. coli, Str. viridans and Staph. albus in the colon; B. mucosus capsulatus predominating with B. coli and B. proteus in the ileum; B. proteus, B. coli, B. mucosus capsulatus and Str. viridans from the peritoneal fluid.

CASE 6 -Baby of E J., born Dec. 17, 1937; weight, 2,840 gm.; normal delivery; initial feeding, evaporated milk mixture, mother was suspected of syphilis, but Kahn test was negative.

Symptoms -On Dec. 24, 1937, sniffling, refusal of the formula, temperature 99.6° F. rectally, and a yellowish loose stool occurred.

There were four to ten stools Course -Transferred to Children's Division daily, many liquid.

Laboratory Findings .- Stool cultures negative for the colon typhoid, salmonella group and B. pyocyaneus.

Diagnosis - Infection of the upper respiratory tract, with secondary diarrhea.

Result .- Discharged cured Jan 22, 1938.

CASE 7 .- Baby of A. M, born Nov. 25, 1937; weight 2,880 gm.; normal delivery; initial feeding, evaporated milk mixture; mother suspected of miliary tuberculosis.

Symptoms - Several slightly watery stools Dec. 28, 1937.

Course -Infant remained in ward nursery for newborn because of mother's tuberculosis, and was transferred to Children's Division Dec. 28, 1937, with three to six stools daily, occasionally liquid. No elevation of temperature, but later reached 102° F. (axillary).

Laboratory Findings -Stool cultures, B. pyocyaneus.

Diagnosis .- Primary diarrhea.

Result .- Discharged cured Jan. 31, 1938.

CASE 8 -Baby of A S, born Dec 23, 1937; weight, 2,900 gm.; normal delivery; initial feeding, evaporated milk mixture; mother diagnosed as having gonorrheal vaginitis.

Symptoms -- None; infant transferred to Children's Division on Dec. 28, 1937, because of closure of the ward nursery.

Course.—Loose stools, temperature 100° F. (axillary), Dec. 29, 1937. temperature reaching 102° F. (axillary), with diarrhea until death.

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, and B. pyocyaneus

Diagnosis - Sepsis of newborn.

Result .- Patient expired Jan 7, 1938.

Autopsy Findings -- Mural endocarditis and verrucous endocarditis of the mitral valves; fibrinous pericarditis; multiple abscesses of both kidneys and myocardium; acute hemorrhagic enterocolitis; passive congestion of all organs

Post Mortem Bacteriology -Staph aureus from the heart blood, staphylococci in the pericardial fluid; Staph aureus and B coli, in the bile; B. coli, Staph, aureus, B. aerogenes and B. proteus in the colon and ileum.

Case 9.—Baby of M O, born Nov. 3, 1937; weight, 3,900 gm; normal delivery; initial feeding, boiled milk mixture; mother had scabies.

Symptoms -None, infant transferred to Children's Division on Dec. 28, 1937, because of closure of ward nursery.

Course.-On Dec. 29, 1937, five stools, one liquid. Thereafter, an occasional liquid stool Temperature norm il throughout.

Laboratory Findings -Stool cultures yielded B. pyocyancus

Diagnosis - Diarrhe L

Result,-Discharged cured Jan 22, 1938,

CASE 10-Baby of J. H., born Nov. 25, 1937; weight, 3,065 gm.; normal delivery; initial feeding, raw breast milk; mother had a positive Kahn test.

Course.—Discharged normal newborn Dec. 27, 1937. Admitted to Children's Division Dec. 29, 1937.

Symptoms -- Watery bowel movements, no elevation of temperature, two to five stools daily, occasionally liquid.

Laboratory Findings.—Stool cultures were negative for the colon typhoid, salmonella group, and B. pyocvaneus.

Diagnosis - Diarrhea.

Result -Discharged cured Jan. 19, 1938.

CASE 11.—Baby of F. P, born Dec 16, 1937; weight, 3,195 gm.; normal delivery; initial feeding, evaporated milk mixture, mother had urticaria and an infection of the upper respiratory tract.

Course.—Discharged as normal newborn infant Dec. 24, 1937. Admitted to Children's Division Dec. 30, 1937.

Symptoms —History of greenish liquid stools for preceding five days. In hospital, three to five stools daily, occasionally liquid.

Laboratory Findings - Stool cultures were negative once and positive once for B. pyocyancus.

Diagnosis .- Diarrhea.

Result .- Discharged cured Jan. 20, 1938.

#### Ward 51 (Normal Obstetrics)

Case 12.—Baby of E. O, born Nov 29, 1937, weight, 4,080 gm.; normal delivery; initial feeding, at breast.

Course.—Transferred to Children's Division Dec. 6, 1937, three to six stools daily, yellowish green color, occasionally semiliquid. Discharged cured Jan. 1, 1938. Readmitted to Children's Division Jan 9, 1938, three greenish, watery stools daily for preceding three days

Symptoms—On Dec. 6, 1937, elevation of temperature 100.6° F (rectally) and several loose stools. On readmission, stools again were liquid.

Laboratory Findings —Stool cultures in both instances negative for colon typhoid, salmonella group, and B. pyocyancus.

Diagnosis—Infection of the upper respiratory tract with secondary diarrhea. Result.—Discharged cured Jan. 1, 1938. Second discharge, cured, Feb. 1, 1938.

Case 13 -Baby of C. D., born Dec 3, 1937; weight, 2,940 gm.; normal delivery; initial feeding, at breast.

Course.—Discharged as normal newborn infant, Dec. 13, 1937. Admitted to Children's Division Dec. 17, 1937.

Sumptoms.—On Dec. 16, 1937, nasal discharge, sneezing, drainage from the umbilicus, loose watery stools occurred. Temperature 107° F. (axillary).

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, and B. pyocyaneus.

Diagnosis.—Infection of the upper respiratory truct; umbilical sepsis, secondary diarrhea.

Result .- Patient expired Jan. 2, 1938.

Autopsy Findings.—Hemorrhagic bronchopneumonia; icterus gravis neonatorum, anemia and degeneration of parenchymatous organs

Post-Mortem Bacteriology, -Cultures from heart's blood, Str. tiridans, from intestine, B. coli and Staph. albus.

CASE 14.—Baby of H. P., born Dec. 5, 1937; weight, 2,858 gm.; normal delivery; untial feeding, at breast.

Symptoms .- Jaundice Dec. 13, 1937, persistent; failure to gain weight.

Course.—Transferred to Children's Division Dec. 18, 1937. Loose stools appeared next day, yellowish green, three to six daily, occasionally liquid.

Laboratory Findings .- Stool cultures yielded B. enteritides.

Diagnosis.-Sepsis of newborn.

Result .- Discharged cured Jan. 8, 1938.

GASE 15.—Baby of T. S., born Dec. 17, 1937; weight, 3,488 gm.; normal delivery; initial feeding, at breast. Mother diagnosed as having scarlet fever Dec. 18, 1937, and transferred to Contagious Division.

Symptoms.-Temperature 101.8° F. rectally, Dec. 21, 1937.

Course .- Transferred to Children's Division Dec. 21, 1937.

Laboratory Findings .- No cultures done.

Diagnosis -- Bronchopneumonia and sepsis.

Result .- Patient expired Dec. 23, 1937.

Autopsy Findings .- Bronchopneumonia.

Post-Mortem Bacteriology.—Cultures, intestinal contents; B. coli, B. aerogenes, Staph, albus and Str. viridans.

CASE 16.—Baby of J. M., born Dec. 15, 1937; weight, 3,165 gm.; normal de livery; initial feeding, at breast.

Symptoms.—Temperature 101° F. (avillary), mass in left upper quadrant Dec. 19, 1937. Stools curded and dyspeptic.

Course.—Transferred to Children's Division Dec. 20, 1937. Liquid stool Dec. 22, 1937, green-yellow, soft, three to four daily.

Laboratory Findings .- Stool cultures yielded B. enteritides.

Diagnosis.-Splenomegaly and sepsis of newborn.

Result .- Discharged cured Jan. 19, 1938.

CASE 17.—Baby of A. K., born Dec. 8, 1937; weight, 2,670 gm.; normal delivery; initial feeding, at breast. Condition fair at birth, placed in ward nursery incubator.

Symptoms.-Persistent jaundice and marked anemia.

Course.—Transferred to Children's Division Dec. 17, 1937. One liquid stool, Dec. 20, 1937, with four to five liquid stools Dec. 23, 1937.

Laboratory Findings .- Stool cultures yielded B. enteritides.

Diagnosis .- Marked physiologic jaundice and sepsis of the newborn.

Result .- Discharged cured Jan. 26, 1938.

CASE 18.—Baby of C. Y., born Dec. 18, 1937; weight, 2,865 gm.; normal delivery; initial feeding, skimmed lactic acid milk.

Symptoms.—General condition poor at birth, limpness, cyanosis, and grunting respirations. Marked jaundice, bleeding from the bladder and umbilical cord appeared four hours after birth.

Course.—Transferred to Children's Division several hours after birth. Mucus noted in stool Dec. 19, 1937, liquid stools Dec. 22, 1937, greenish yellow, five to seven daily.

Laboratory l'indings.—Stool cultures negative for the colon typhoid, salmonella group, and B. pyocyancus. Icteric index mitially 90, dropped to 15.

Diagnosis,--Suspected erythroblastosis fetalis.

Ecsult .- Discharged cured, Jan. 26, 1938.

CASE 19.—Baby of H. B: born Dec. 13, 1937; weight, 2,790 gm.; frank breech presentation; initial feeding, raw breast milk.

Symptoms - Jaundice appeared Dec 23, 1937; and became exaggerated.

Course—Placed in isolation nuisery Dec 23, 1937, mucoid stool, Dec. 24, 1937. green watery stool, Dec. 25, 1937. Transferred to Children's Division on latter date. There were three to six stools daily, some liquid.

Laboratory Findings -- Stool cultures negative for the colon typhoid, salmonella group and B. pyocyaneus

Diagnosis - Physiologic jaundice and sepsis of newborn.

Result - Discharged cured, Jan 18, 1938.

CASE 20.—Baby of E B, born Dec. 15, 1937; weight, 3,525 gm; normal de livery, initial feeding, at breast

Symptoms -Two pustules noted in right gioin Dec 21, 1937.

Course.—More lesions of similar character subsequently and watery stools Dec. 25, 1937. Infant transferred to Children's Division on that date. There were two to six stools daily, semiliquid and sometimes curded.

Laboratory Findings -Stool cultures negative for colon typhoid, salmonella group, and B pyocyaneus.

Diagnosis -Impetigo and sepsis of the newborn.

Result .- Discharged cured Jan 26, 1938.

CASE 21.—Baby of R. G, born Nov. 13, 1937, weight, 3,180 gm.; normal delivery; initial feeding, evaporated milk mixture.

Symptoms.—Marked bleeding from the cord several hours after birth. Jaundice, cyanosis, general condition poor.

Course—Whole blood (15 c.c.) given intramuscularly. Transferred to Children's Division, Nov. 14, 1937. On Dec. 21, 1937, two semiliquid stools and after Dec. 24, 1937, three to five liquid stools daily.

Laboratory Findings -Stool cultures yielded B. pyocyaneus. Icteric index 180 initially, dropped to 15.

Diagnosis - Marked physiologic jaundice and sepsis of newborn.

Result.-Discharged cured Jan. 19, 1938.

CASE 22—Baby of M S, born Dec. 19, 1937; weight, 3,210 gm.; normal de livery; initial feeding, at breast

Sumptoms -Several liquid stools Dec. 25, 1937.

Course - Transferred to Children's Division Dec. 26, 1937. Semiliquid and liquid greenish yellow stools, four to six daily.

Laboratory Findings -Stool cultures yielded B. pyocyaneus.

Diagnosis -- Diarrhea

Result.-Discharged cured Jan. 27, 1938

CASE 23 -Baby of P. P., born Dec. 18, 1937; weight, 2,805 gm.; normal de livery; initial feeding, at breast.

Symptoms - Redness and swelling of the left lower eyelid Dec. 24, 1937.

Course -Transferred to Children's Division Dec. 24, 1937; green semiliquid stools Dec. 27, 1937, thereafter, three to six loose stools daily.

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, and B. pyocyaneus.

Diagnosis - Dicryocystitis and sepsis of newborn.

Result .- Discharged cured Jan. 25, 1938.

CASE 24 —Baby of L Sa., born Dec. 19, 1937; weight, 3,210 gm.; normal de livery; initial feeding, at breast.

Symptoms — Temperature 1004° F. (anillary), regurgitation of formula, loose stool Dec. 26, 1937. Liquid stool Dec. 27, 1937.

Course -Transferred to Children's Division Dec. 27, 1937.

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, and B. pyocyaneus.

Diagnosis .- Sepsis of newborn.

Result .- Discharged cured Feb 1, 1938.

Case 25.—Baby of B W., born Dec. 4, 1937; weight, 2,615 gm; normal delivery, initial feeding, at breast.

Course.—Discharged normal newborn Dec. 11, 1937. Admitted to Children's Division Dec. 31, 1937.

Symptoms.-Watery stools, two to four daily for preceding four days.

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, B. pyocyaneus.

Diagnosis - Diarrhea

Result .- Discharged cured Jan. 19, 1938.

Case 26.—Baby of M. de M., born Dec. 19, 1937; weight, 3,630 gm.; normal de livery; initial feeding, at breast.

Course - Discharged normal newborn Dec 27, 1937. Admitted to Children's Division Jan 2, 1938.

Symptoms — Yellowish mucous stools, four to six daily for preceding five days Redness of eyes for same period.

Laboratory Findings -- Successive cultures yielded a different microorganism each time-B. enteritides, B. pyocyaneus, B. coli. Smears from the eye were negative for pathogenic organisms.

Diagnosis - Bilateral conjunctivitis and secondary diarrhea.

Result .- Discharged cured Jan. 27, 1938.

CASE 27.—Baby of A P, born Dec. 24, 1937; weight, 3,390 gm.; normal de livery; initial feeding, at breast.

Course —Discharged normal newborn Jan 3, 1938. Admitted to Children's Division eight hours later.

Symptoms—Yellowish green liquid stools, three to six daily. Temperature 104° F. (axillary). Diffuse maculopapular eruption and bilateral conjunctivitis noted Jan. 5, 1938.

Laboratory Findings -Stool cultures negative for the colon typhoid, salmonella group, and B pyocyaneus Eye smears negative for pathogenic organisms

Diagnosis - Sepsis of the newborn and bilateral conjunctivitis.

Result .- Discharged cured Jan 27, 1938.

A survey was made of all potential foci from which the epidemic might have originated. It was found that the attending staff, five obstetricians and five associates, served the three wards as called upon for delivery. Patients were delivered and visited in all wards by all members of the staff. A resident was assigned to each ward; those of Ward 50 (operative) and of Ward 51 (normal obstetrics) relieved each other every second night by assuming both services. The resident on Ward 41 did not exchange services with either of the other

TABLE 1 DIET, TREATMENT AND RESULTS

I c	RESOLA		Cured	Cured	Cured	Death	Donth	Death	Death	Denth	Cured	Curron	on co	Carea	Death			Cured	Cured	Death	Curod	Curred	Cured	Cured	Cured	Cured	Cured	Death	Cured	Cured	Cured	Cured	Cured	Cured	4
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Key to Table I: Arr., artificial; B.B.M., boiled breast milk; Br., breast; B.T., blood transfusion; Clysis, hypodermociysis; D & S, dectroes (2.1/4.°) and saline (6.1%) solution; Eyar, evaporated milk; H. & D, Hartmann's dextrose solution (2.1/4.%); Inravenous; N.B. Nir., newborn nursery; P.P.M., powdered protein milk; R.B.M., raw breast milk; S.L.A.M., skimmed lactic acid milk; +, given; -, not given.

# LABORATORY FINDINGS

TABLE II

	STOOL	BL00D	B.A.P.	URINE	R.B.C.	W.B.C.	% gii	TEMP.	PATH, IN MOTHER	RESULT
NAME	CULT.	CULT.								
WARD 41						-	-	Z	Scabies	Cured
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J. M.*	B. Ent.	N.G.	0	0		5.77	3.5	200	<b>&gt;</b> •	Don'th
T. S.		!	1	0	<del>1,</del>	4.7	08	2010	> <	Cean
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M. de M.*		λ.C.	0	0	5.3	7.7	98	3. E.	0	Cured
	B. Coli								,	,
I. Sa.*	_	S.A.	0	0	5.0	13.2	93	S. S.	<b>~</b>	Cured
M. S.	B. Pyo.	A.C.	0	0	4.2	6.9	78	S.E.	<b>3</b>	Cured
A. P.			,	,		0	ç	ŭ O		المستوط
	B. Pyo.	N.G.	0	0	4.0	9.8	60	9.5.		Oaten
*Blood agg	*Blood agglutination negat	gative for cold	ive for colon typhoid, salmonella group, and B. pyocyaneus,	Ilmonella grou	ip, and B. py	ocyaneus.				

\*Blood agglutination negative for colon typhoid, salmonella group, and B. pyocyaneus.
Key to Table II: A.C., air coccus: B.A.P., blood agar plate; B. Enr., B. enteritides; B. Pro., B. pyocyaneus; B.S., B. subtilis; Gc., gonorrhea; N.G., no growth; S., septic; S.A., Staph. aibus; U.R.I., infection of upper respiratory; Unr., urticaria; 9, negative; -, not done.

two, but a fourth resident, assigned to the prenatal clinic and not working in the first two wards, relieved him every second night. The four internes assigned to Ward 50 and Ward 51 exchanged services. The two internes on Ward 41 served their own ward only. None of the obstetric staff entered the newborn nurseries. The same attending pediatrician, resident, and interne from the pediatric department supervised all nurseries.

The nursing personnel in each of the three obstetric wards was specifically assigned to labor rooms, care of prepartum and postpartum ward patients, and the newborn infant nurseries. There was no interchange of duties and no shifting of nurses from one ward to the other. Nurses assigned to the nursery were instructed in the thorough cleansing of hands with soap and water before handling infants. The appearance of any skin lesion, abrasion, or disease in a nurse assigned to the care of the newborn infants, prohibited her from work in the unit until all symptoms had disappeared. No nurse was allowed to work in the nursery unless her nose and throat cultures were negative for hemolytic streptococci.

Infants of Wards 50 and 51 received nothing by mouth for the first eight hours and then, if the mother's condition permitted, were put to breast on a four hour schedule. Complemental feedings of raw breast milk or whole boiled or evaporated milk were offered to those who obtained an insufficient amount. On Ward 41 the feeding of the infants of mothers with normal temperature and negative serology was the same as on the other two wards. The infants of mothers with positive serology were put to the breast only if the routine x-ray examination of the long bones showed evidence of syphilis in their progeny. For the two or three days pending the x-ray report, these infants were given evaporated or whole boiled milk. Water and tea were offered between feedings to the infants on Wards 51 and 41, but not to those on Ward 50.

The complemental and supplemental feedings were prepared in the milk laboratory in the Children's Hospital, a separate building. Ward 51 received its formulas in quart bottles which were poured into individual nursing bottles in the obstetric ward kitchen. A complete sterile setup including a scrubbed nurse was part of the routine procedure in the ward. The water offered to the infants between feedings came from sterilizers in the obstetric ward and was poured into feeding bottles previously boiled in the obstetric ward kitchen.

Table III is a schematic representation of the ward routines. It will be noted that:

- 1. Nurseries of Wards 51, 50, and 41, were served by the same attending obstetric and pediatric staff.
  - 2. Infants in Wards 51 and 41 only were infected; Ward 50 escaped.

- 3. The same residents served Wards 50 and 51 but only Ward 51 was infected.
- 4. Ward 41 was served by a separate set of residents, and it was infected.
- 5. No interchange of nursing personnel occurred in the three nurseries.

TABLE III

COMPARISON OF TECHNIQUE IN OBSTETRIC WARDS

		<del></del>	
	NORMAL OBSTETRICS	OPERATIVE AND NON- INFECTIOUS COM- PLICATIONS	VENEREAL AND OTHER INFECTIONS
	WARD 51	WARD 50	WARD 41
	INFECTED	NOT INFECTED	INFECTED
NURSES	INDIVIDUAL	INDIVIDUAL	INDIVIDUAL
Obstetrics			
Att. Obst. Resident	Same INTER	Same CHANGE	Same Individual
Interne	INTER	CHANGE	Individual
Pediatrics Att. Ped. Resident Interne	Same Same Same	Same Same Same	Same Same Same
Milk formulas	Prepared in Chil dren's Hospita diet kitchen but poured in obstetric kitchen.	Prepared and poured in Children's Hospital diet kitchen.	Prepared and poured in Children's Hospital
Water	Prepared and poured from ster- ilizer in obstetric kitchen	•	Prepared and poured in Children's Hospital diet kitchen.

It seems reasonable to conclude from the above analysis that the infection was not transmitted by members of the medical staff or nursing personnel.

Reports from the bacteriologic laboratory yielded the following information:\*

#### A. Mill:

- 1. Evaporated.—No growth was obtained from a can opened in the bacteriologic laboratory. Random samples taken in the course of preparation of formulas yielded hay bacillus, unclassified streptococci, and Str. ciridans, each once. Five days after the outbreak, a sample of the milk and water formulas prepared by Ward 51 contained B. pyocyaneus and Str. ciridans. This prompted an immediate elimination of formula preparation in the obstetric ward kitchen. Subsequent formulas were prepared a professional Color.
- 2. Pasteurized.—Cultures of the pasteurized bottled milk as delivered by the dairies yielded gram-negative rods, Staph. albus, and Str. viridans on various occasions. B. pyocyancus was reported twice.

<sup>\*</sup>The bacteriologic studies were done by Miss Carrie I. Woolsey, M.A., Department of Bacteriology, Cook County Hospital, without whose cooperation, this report would

- 3. Rau breast milk Cultures reported only an occasional Staph. albus
- B Sugar
  - 1. Canc.—The hay bacillus was isolated.
  - 2 Karo -Staph albus and the hay becillus were isolated.
- C. Water. A number of samples contained Staph albus and the hay bacillus. A sample from Ward 51 yielded B. pyocyaneus on Dec. 12, 1937.
- D. Miscellancous
  - 1. Fmpty capped nursing bottles from sterilizer—Hay bacillus and Staph. albus.
  - 2 Fmpty bottles from sterilizer.—Hay bacillus
  - 3 Corls for nursing bottles-Heavy growth of B. pyocyaneus.
  - 4 Tea-No growth of organisms
  - 5. Dust.—This was collected from a cupboard in the milk laboratory and yielded B. pyocyaneus
  - 6 Simmon's plate Exposed two hours in the milk laboratory, no growth.
  - Simmon's plate—Exposed two hours in the kitchen of Ward 51, one colony of B pyocyaneus
  - S Blood agar plate -- Exposed two hours in the milk laboratory with a growth of twenty four colonies of contamination organisms, no strepto cocci.
- E\* Stools Stool cultures were done in twenty two of the twenty seven cases. Two or more cultures were done in most cases. B enteritides was found in three, B. pyocyancus in six, and in one case three cultures each yielded a different organism, namely B enteritides, B pyocyancus and B coli In twelve cases, none of the organisms commonly associated with enteric disturbances were isolated.
- F.\* Blood. Blood cultures were done in nine cases, several being chosen from the various groups as evidenced by stool culture reports. There were five reported as "no growth," two contained an air coccus (contaminant), one had a growth of B. subtilis (contaminant), the remaining one yielded Staph. albus Those reported as air coccus and B. subtilis may be regarded as negative

Agglutination of the blood for the colon typhoid group including B. pyocyancus was done in seven patients, again using cases from the various groups. All were reported as negative

G \* Nove and Throat Cultures Smears from the nose and throat of all infants in this series were plated on blood agar medium and yielded two positive cultures for the hemolytic streptococci. These were reported as four plus. Subsequent cultures became negative and both recovered.

The clinical laboratory findings were as follows.

- 1 Urmalusis \*-A mild albuminuma occurred in four children, the remainder being negative.
- 2. Blood Count.\*—The red blood count varied from 2,740,000 to 6,170,000. The white count ranged from 5,750 to 30,500 with the latter figure occurring in an infant with suspected crythroblistosis fetalis. The hemoglobin determinations scaled from 52 per cent to 110 per cent according to the Tallqvist method.
- Maternal Pathology.—All infants born on Ward 51 had mothers entirely free from recognized pathologic conditions. All infants born on Ward 41 had mothers with such pathologic conditions as positive Wassermann test, mild upper respiratory infection, gonorrhei, or scabies

TA	BLE IV	
SUMMARY OF	STOOL	CULTURES

				NEG. FOR COLON TYPHOID	NO CULTURE
WARD	B. ENT.	B. PYO.	B. COLI.	NEG. FOR COLON TYPHOID SALMONELLA GROUP	NO COMORE
					9
11	0	5	0	ð	2
41	U	v	**	-	٦.
		2	7	9	1
51	4	<b>(3)</b>			
_~~ .	-	ρ	7	7.1	3
Total	4	Ø		12	
4.0000	-				

NOTE: MdM. 3 stool cultures, each yielded a different organism.
A.P. } 2 stool cultures, each yielded different organisms.

A review of contaminating organisms of which one might be suspicious in such an epidemic revealed the following:

- 1. B. pyocyaneus was reported in the dust of the milk laboratory, supplying all wards after Dec. 12, 1937.
- 2. B. pyocyaneus was recovered from the bottle corks sent to Wards 50 and 41.
  - 3. B. pyocyaneus was recovered from the water supply of Ward 51.
- 4. B. pyocyaneus was recovered from the formulas after pouring in the kitchen of Ward 51.
- 5. Other contaminants were found less frequently in the utensils and food used in these wards.

In spite of these findings, Ward 50, equally subjected to contamination, escaped the epidemic. One hundred and two infants in this ward were given formulas prepared in the milk laboratory with no ill effect, in contradistinction to the result in Ward 41 where eleven of twentynine infants fed identical formulas became ill.

These findings suggest that, despite the reported frequency of B. pyocyancus as a contaminant of the food and water supply, one cannot conclude with assurance that it was the causative agent, since of two wards whose food supply was derived from the same source only one was affected.

Furthermore, it is unlikely that the infection could have been derived from the water supplied to the newborn infants since Ward 51 (infected) used water from their own sterilizer and Ward 41 (infected) received its water from the milk laboratory. It is interesting to note, however, that Ward 50 (not infected) gave no water to its infants; however, it gave complementary feedings containing water from the same milk laboratory that supplied the other two wards.

Table V is a summary of the autopsy findings in the seven who died. The procedure employed in the control of this epidemic followed the usual routine of our newborn infant nurseries. Within twelve hours of the initial sign of illness in the first infant (Case 12), he was transferred to the Children's Division and isolated. Each succeeding ease was transferred as soon as there was a suspicion of illness. Twenty-four infants became ill between Dec. 6, 1937, and Dec. 28, 1937, before it was recognized that the nurseries had to be closed in order to stamp

out the infection. During this period new cases occurred at irregular intervals. After a lapse of several days without new cases developing, a false sense of security was disrupted by the appearance of a new case. During this period the bacteriology of the food, water, and personnel was carefully investigated and resulted in the findings recorded above. It was deemed advisable because of the bacterial contamination to centralize the preparation of food in the diet kitchen of the children's division. This eliminated any source of infection which might have occurred from food and water prepared in the newborn nurseries. In spite of this change in procedure, however, the epidemic continued.

TABLE V
SUMMARY OF AUTOPSY REPORTS

MULTIPLE ABSCESSES 2		BRONCHO- PNEUMONIA 6		ENTERO- COLITIS 2		ENDO- CARDITIS 1
			Bacteriology	,	~	
			Heart's Bloc	od		
Str. viridans		B. muc, cap.		$B.\ coli$		Staph. aureus
1		1	Gastrointestir	nal		1
B. coli 5	Staph. albus 3	Staph. aureus 1	B. muc. cap. 2	B. pyo.	B. prot,	Str. viridans 2

On Dec. 28, 1937, both nurseries were closed, and the remaining six well infants were transferred to the Children's Division. Three of these became ill the following day, and one died (endocarditis).

The newborn ward was thoroughly cleaned and repainted and not opened for a period of two weeks.

All three wards have been in use continuously for the past fourteen months, during which time not a single case in any way resembling these has occurred.

#### DISCUSSION

A review of the findings at autopsy showed bronchopneumonia in six of the seven infants who died, and in only two was there anatomic evidence of enterocolitis. Multiple abscesses were found in two and endocarditis in one. Table V shows the large variability in the bacteriologic findings of the heart's blood and gastrointestinal tract at post mortem. When compared with the bacteriology reported from the stools and blood during life (Table II), it is evident that no correlation can be determined.

Rice and his associates<sup>1</sup> tabulated the bacteriologic reports in five epidemies from various cities. Each reported a different organism and in several epidemics, more than one organism predominated in

the stools. In the same paper they reported 505 cases of neonatal illness in sixteen epidemics in New York City and state that "numerous cultures of the stools and of the nasal and pharyngeal secretions of the sick infants gave very indefinite results. Similar cultures taken from the nurses, physicians, mothers, and other maternity and nursery service personnel also failed to reveal a causative organism."

In the New York epidemics reported by Rice and his co-workers, 234 of the 505 infants infected died, a mortality rate of 46 per cent. They showed that the fatality rate was 44 per cent in eight other epidemics occurring elsewhere. In our epidemic, death occurred in seven of twenty-seven infected infants, a fatality rate of 26 per cent.

The control of an epidemic of sepsis in a newborn ward is based upon recognition of the first case and closure of that ward until all contacts have been dismissed and the wards thoroughly cleaned before reopening.

#### CONCLUSION

Serious epidemics of sepsis have occurred in the newborn nurseries of many institutions. These epidemics are accompanied by a fatality rate varying between 0 and 79 per cent, the average being between 40 and 50 per cent.

The method of transmission and dissemination of infection has not been determined.

The etiology of these epidemics cannot be ascribed to a single causative agent in view of the variability of bacteriologic reports.

Epidemics have been best controlled by immediate closing and cleaning of the infected nursery and admitting no new infants until all contacts have been discharged.

In view of the post-mortem findings in this, as well as in similar epidemics elsewhere, it seems desirable that such epidemics be classified as "sepsis in the newborn infant" rather than diarrhea, until a definite etiological agent can be isolated.

The prevention of similar epidemics is based upon the most vigorous aseptic technique in the management of the newborn nursery. This technic must include exclusion of all infected individuals from the nursery and the limitation of all unnecessary handling of the newborn infants.

No specific therapy is suggested. Raw human milk feedings, whole blood, and parenteral fluids are indicated as prophylactic and supportive measures.

#### REFERENCE

Rice, J. L., Best, W. H., Frant, D., and Abramson, H.: J. A. M A. 109: 475, 1937.

<sup>185</sup> NORTH WARASH

#### STAPHYLOCOCCUS PNEUMONIA

A CLINICAL, PATHOLOGIC, AND BACTERIOLOGIC STUDY
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VERY little has been written about staphylococcus pneumonia as a disease. Chickering and Park<sup>1</sup> in 1919 and Reimann<sup>2</sup> in 1933 each reported several cases in adults. Four cases in children were reported by Smith,<sup>3</sup> but these terminated before the complete clinical picture had developed. MacGregor<sup>4</sup> described ten cases of staphylococcus pneumonia which were also fatal. No differentiation into primary and secondary pneumonia was made. Recently Anderson and Catheart<sup>5</sup> reported a case which they considered primary. Other papers on the subject dealt with staphylococcus pneumonitis secondary to virus diseases, such as influenza or pertussis.

In this paper we are presenting thirty-seven cases of pneumonia in which the staphylococcus organism was the etiological agent. These cases we classify as follows:

- 1. Primary staphylococcus pneumonia.
- 2. Secondary staphylococcus pneumonia occurring in the course of a staphylococcus sepsis.

We have been especially interested in the first group. In these cases the pneumonia was the outstanding feature of the illness and dominated the clinical picture. The symptoms and the findings on physical examination closely resembled, in most instances, those found in pneumococcus pneumonia. At autopsy, however, the lungs showed infection typical of staphylococcus pathology, e.g., tissue destruction and abscess formation. Empyema was an almost constant complication.

In the second group the clinical picture was that of sepsis with a readily demonstrable extrapulmonary primary focus in the majority of cases. Most of the patients, however, did develop symptoms and signs of pneumonia at some time during the course of the sepsis with complete overshadowing of the other findings. In a few the pneumonia remained subsidiary, and the evidence of lung involvement was sparse.

In the first group there were twenty-five cases, or 68 per cent of the total. In the second group there were twelve patients, and in eight of these the pneumonia overshadowed the sepsis during some phase of the course.

From the Departments of Pedlatrics and Pathology, Jewish Hospital of Brooklyn.

#### BACTERIOLOGY

The etiology in our cases was determined in one of three ways: by blood culture, culture of the empyema fluid, or by culture of the lung at autopsy. Our figures do not include cases, if they exist, which recover without having developed either bacteriemia or empyema.

The blood culture was positive in four of the twenty-five primary cases (16 per cent), but only one of these was positive during life. And in this one only the broths showed organisms, while in the three positive post-mortem cultures, there was massive invasion of broths and agar plates.

Of the patients in the secondary group, all had positive cultures during life. Ten of the twelve had massive blood stream invasions (more than ten colonies per cubic centimeter of blood); one had a moderate invasion (one to ten colonies); and one showed a slight invasion (broths positive, plates sterile).

In all instances the staphylococcus was in pure culture when isolated from the blood or empyema fluid. Post-mortem specimens showed the organism either in pure culture or predominating.

#### ETIOLOGY

Season.—Our cases of primary staphylococcus pneumonia followed the seasonal incidence of other types of pneumonias. They differed in this respect from other forms of staphylococcus infection. Eighty per cent of the primary cases developed during the winter and early spring, whereas only 20 per cent occurred during the summer season. On the other hand, 60 per cent of the secondary cases came during the summer months, following closely our experience in a previous study of staphylococcus bacteriemia. There was no tendency to occurrence in epidemics (Tables I and II).

MONTH PRIMARY SECONDARY STAPH. SEPSIS Jan. 2 4 Feb. 2 0 2 March 7 0 6 2 6 April 0 1 May 1 3 June 1 0 411 20022 July 0 Aug. 2 Sept. 221 4 Oct. 4 Nov. 6 Dec.

TABLE I
DISTRIBUTION OF CASES BY MONTH

Scr.—The primary cases were equally distributed between males and females. Secondary pneumonia, however, was twice as frequent in males, which was also true of cases of staphylococcemia previously studied (Table III).

'	L ibi f	11		
DISTRIBUTION	OF CY	SFS S	SEASONA	LLY

SE150V P	RIMARA (ASES	SECONDARY CASES	STAPH. SEPSIS
J. F. M			
O. N. D.	19	5	28
7. M. J.	_	<b>~</b>	10
J. A. S. % Cases coming in uinter	50%	6164	18 61%
% Cases coming in summe		63% 57%	59%

TABLE III
DISTRIBUTION OF CASES ACCORDING TO SEX

	PRIMARY CASES	SFCONDARY CASES	STAPH. SEPSIS
Male	12	8	30
Female	11	4	15

Age.—Seventy per cent of the primary pneumonias occurred in patients under one year of age. 21 per cent at from one to five years, and only 9 per cent were over five years of age. Of the secondary cases only 46 per cent occurred in children under one year of age, 22 per cent between one and five years, and 32 per cent were in children over five years of age. Again, the secondary cases followed an almost identical distribution as in our patients with staphylococcemia (Table IV).

TABLE IV
DISTRIBUTION OF CASES ACCORDING TO AGE

AGE (1R.)	PRIMARY CASES	SECONDARY CASES	STAPH. SEPSIS
Under 1	16	5	21
$1\ 2$	2	0	2
$2\ 3$	2	3	5
3 5	1	1	3
<b>5</b> 9	1	2	12
Over 9	1	1	2
% under 1	70	41	$\frac{3}{46}$
% over 5	9	25	32

In our cases the weight and development were good except where the pneumonia started after a long and debilitating illness (Table V). We found no other predisposing factors.

TABLE V
BIRTH WEIGHTS IN THE TWO TYPES

WEIGHT AT BILTH	PLIMALY CASES	SECONDARY CASES
Under 6 lb.	3	0
6 lb. to 16 lb. 15 oz.	5	Ŝ
7 lb. and over	ປ໌ ຄ	4
Unknown		<u></u>

#### CLINICAL PICTURE

Onset.—The onset of the primary pneumonias was fulminating, acute, or insidious. In eighteen cases the pneumonia began acutely, follow-

ing a banal upper respiratory infection of twenty-four to forty-eight hours' duration in ten, a more or less chronic upper respiratory infection in seven, and a long period of diarrhea and intestinal intoxication in one. The onset was fulminating in four eases, with a rapidly developing lung infection reaching its climax in only a few hours, without any prodromes. In two cases the onset was insidious, the pneumonia starting gradually in the course of a prolonged, mild upper respiratory infection.

There was no distinctive symptom that could be considered characteristic of the onset. In one primary case and in two secondary cases the illness was ushered in by a chill.

Fever.—Of the twenty-three cases with primary pneumonia, eight had a high sustained temperature, and two showed low sustained temperature. Ten of the twenty-three cases therefore developed a fastigial fever curve which is commonly associated with pneumonia and is usually attributed to the pneumococcic type of infection. Seven cases showed a high, irregular curve and one, a low grade irregular fever. Four had low or normal temperatures. We considered the temperature high if above 103° F., moderate if below 102° F., and sustained if the diurnal variation was less than one degree.

We believe that in any group of pneumonias caused by other organisms the same types of variation would be found. There is one difference however. A patient with pneumococcus pneumonia who shows a low, irregular temperature usually recovers quickly without displaying toxic signs. Such a temperature curve, however, in a patient with staphylococcus pneumonia often spells a long course, terminating in death.

Type of Involvement.—We are concerned with the types of consolidation rather than with a detailed account of the physical findings. Eighty per cent of the twenty-three cases of primary pneumonia presented the physical and x-ray signs typical of lobar pneumonia, and the remainder, those of bronchopneumonia. It is interesting to note that two of the twelve secondary cases also showed a lobar type of involvement. The terms lobar pneumonia and bronchopneumonia are used to describe the clinical picture and do not imply a pathologic classification. As a matter of fact, autopsy revealed scattered foci of lobular consolidation in some of the cases where the clinical and x-ray criteria indicated a lobar pneumonia.

Empyema.—Empyema occurred with such frequency in our cases that it might be considered an integral part of the disease rather than a complication. We saw it in 87 per cent of the primary cases and in 58 per cent of the secondary cases. To these may be added a patient with primary pneumonia who developed a sterile, serous effusion.

Although it is impossible to estimate accurately the time of onset of the empyema from the history, our impression is that it came early.

In fifteen cases where a rough approximation could be ventured, the average time of onset was on the sixth day after the beginning of pneumonia.

The color of the empyema pus was distinctive in some of the cases. The pus was described as pink or reddish in three cases, brown in two cases, and chocolate colored in a sixth. In the others the nature of the exudate was not characteristic, appearing either thick yellow or white or greenish, and in one case as seropurulent. In the first six cases we feel the distinctive colors indicated breaking down of tissue with bleeding into the pleural cavity.

Pyopneumothorax.—Spontaneous pneumothorax occurred only twice before chest aspiration had been attempted: in a baby girl of 7 months who died and in a girl of 30 months who recovered.

Upper Respiratory Tract Involvement.—Infection of the upper respiratory tract was a prevalent concomitant finding in the primary cases, but in the secondary cases it was only moderately frequent and never severe. Eighteen, or 80 per cent, of the primary cases had a definite acute pharyngitis. In eight of these the pharyngitis was very severe, one showing actual necrosis of the pharynx. Nine of the children (40 per cent) had acute middle ear infections. In the secondary cases four, or 33 per cent, showed a mild acute pharyngitis and only two (17 per cent) had otitis media.

Three of the primary cases presented a marked purulent nasal discharge, one accompanied by a definite sinusitis. One of the patients in the secondary group also had a sinusitis. Acute adenitis occurred in only one child in the entire series, a child with secondary pneumonia.

Distant Localizations.—Pyogenic localization outside the respiratory tract did not occur in any of the primary cases. Among the twelve secondary cases, however, five developed osteomyelitis; seven had multiple pyogenic skin infections; two developed metastatic foci in the peritoneum; and two developed abscesses in the kidneys.

Gastrointestinal Symptoms.—In the primary group abdominal distention was present in eleven cases, moderate or severe diarrhea in nine, abdominal pain in one, persistent vomiting in one, and gastrointestinal intoxication in one. The gastrointestinal symptoms in the secondary cases were also quite prominent and distressing except for the noteworthy fact that diarrhea did not occur in this group. Our impression is that gastrointestinal symptoms are much more prominent in staphylococcus pneumonia than in pneumococcus infection. In pneumococcus pneumonia distention occurs only in the very severe cases, and diarrhea only rarely.

Genitourinary Tract Involvement.—Six of the patients (25 per cent) with primary pneumonia suffered from involvement of the genitourinary tract. In four patients varying amounts of albumin ap-

peared in the urine; in one there was clinical and laboratory evidence of acute nephritis; and in the sixth ureteritis was found at autopsy. Among the secondary pneumonias there were two with perinephritis. Three of the patients in the secondary group died before renal study could be made, and they were not autopsied. Therefore, 33 per cent of the secondary cases in whom the urinary status was known showed some type of involvement.

Circulatory System.—Cyanosis was a prominent symptom in all groups. It appeared at one time or another in eighteen of the primary cases and seven of the secondary cases. In one primary case and in one secondary case transient murmurs at the precordium were elicited.

Nervous System.—Symptoms of nervous system involvement occurred infrequently (about 12 per cent of all cases) and were not distinctive for either group. Delirium, drowsiness, and meningismus were the usual manifestations, when present. On autopsy there were two instances of intense cerebral congestion (primary cases), one cerebral hemorrhage and one case of toxic encephalitis (secondary cases).

Hematopoictic System.—No special hematologic studies were made. We present the results gleaned from routine studies performed on patients with primary staphylococcus pneumonia. The total white blood cell count varied considerably. In two patients there was a leucopenia of 3,000 and 4,000 cells. Three gave a normal count, seven showed a moderate leucocytosis up to 20,000 white cells; in three the white cell count was above 20,000, and in seven it was above 30,000.

The relative percentage of the polymorphonuclear cells was high in only a few cases: four of the cases gave a percentage of 60; five were under 60 per cent; and thirteen were above 70 per cent. There was, however, a high proportion of immature cells in most smears. This proved to be of importance in the prognosis.

Hemoglobin studies could not be made accurately due to the fact that most of the patients received one or more transfusions during the course of their illness. A Sahli hemoglobin determination was made on each admission and was usually low: only eleven of the twenty-three primary cases showed a reading above 70 per cent.

Duration.—In the primary cases the average duration of the illness in those who recovered was twenty-nine days, and ten days in patients who died. We found these figures similar to those in our series of cases of staphylococcus sepsis.

Prognosis.—Seventy-three per cent of our patients with staphylococcus pneumonia died. The mortality was 65 per cent in the primary group and 83 per cent in the secondary group. This is a high mortality especially when compared with our figures of 56.6 per cent mortality in cases of staphylococcus sepsis.

Infants under 1 year of age suffered the highest mortality and accounted for most of the deaths. Seventy per cent of the patients who

developed primary pneumonia under one year of age died. With secondary pneumonia the mortality was 100 per cent during the first year of life.

A high, sustained fever curve may be considered indicative of a poor prognosis, but an irregular curve, whether at a high or a low level, was usually associated with a favorable outcome. Of the fifteen patients with primary pneumonia who died, nine had a high sustained (fastigial) temperature, two had an irregular temperature with high peaks, and one had a moderate irregular curve. On the other hand, of the eight patients with primary cases who recovered, only one had sustained temperature elevation.

Of the eight patients with primary pneumonia who recovered, seven had signs of a lobar consolidation, and only one had a bronchopneumonic type of involvement. On the other hand all the patients who suffered from lobular types of infection died.

The blood count was an important guide in prognosis. No patient with a low or normal white cell count recovered. The hemoglobin content seemed to have no bearing on the prognosis.

From our analysis we may conclude that staphylococcus pneumonia is a disease in which the mortality is high and in which the patients who recover are sick for a long time. The factors that indicate an unfavorable outlook are infancy (onset under one year of age), an antecedent debilitating disease, bronchopneumonic type of involvement, and leucopenia.

#### PATHOLOGY

Nine of the primary and nine of the secondary cases came to necropsy. The study of the post-mortem picture corroborated the classification into primary and secondary pneumonia. In the primary cases the pathology was confined essentially to the lungs. In the secondary cases there were in addition suppurative foci in other parts of the body. The structures involved, in their order of frequency, were the bones, kidneys, myocardium, adrenals, pancreas, and the voluntary striated muscles. In the primary cases the findings pointed to a bronchogenic origin of the infection. In the secondary cases no matter how extensive the destruction of the lung parenchyma was, it was not difficult to find evidence that this was secondary in nature, as indicated by the presence of infected thrombi in the blood vessels, surrounded by areas of infarction and abscess formation.

The picture in most of the primary cases was quite typical. On opening the pleural cavity the lungs were usually found bathed in purulent fluid of a creamy, greenish color or a reddish or chocolate color. In seven instances there were adhesions between the parietal and visceral pleura. The pleura was thickened, frequently shaggy, and of a gray color. The surface of the lung, especially over a lower

lobe, was studded with small mulberry-like yellowish nodules, "carbuncles," from which creamy pus could be evacuated. The cut surfaces revealed many more of these small abscesses (Fig. 1). In two cases there were a few small foci in the opposite lung.

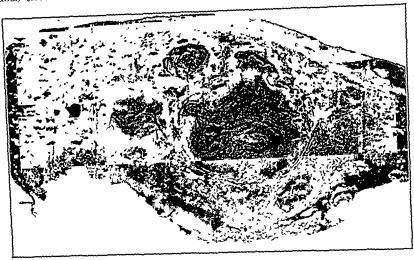


Fig. 1 .- Cut surface of lung.

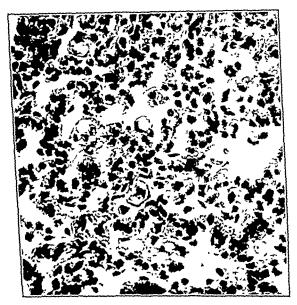


Fig. 2,-"Lipoid" cells (X800).

Microscopic Examination.—There were numerous fairly well circumscribed areas in which the lung architecture was absent, and the centers were made of polymorphonuclear leucocytes. From a little to a moderate amount of fibrin was present in the surrounding zone of parenchyma. Here, the alveoli were filled with polymorphonuclear

leucocytes, few mononuclear cells, and red blood cells. In one instance, this area was markedly emphysematous, and in another the alveolar walls were collapsed. In another case the alveoli contained large pale cells filled with vacuoles, which stained with sudan III (Fig. 2).

The bronchi and bronchioles were filled with polymorphonuclear leucocytes. In some places the bronchial mucosa was absent, the walls infiltrated with leucocytes and mononuclear cells, the capillaries in the walls numerous and distended with red blood cells. Frequently these terminal bronchi communicated with an adjoining abscess.



Fig. 3.-Purulent bronchitis (X67).

A somewhat different picture presented itself in one of this group. The pleural cavity contained considerable cloudy hemorrhagic fluid. The pleura over the left lower lobe was thickened and shaggy. The left lower lobe was almost entirely solid. There were firm nodular areas in the remaining lobes. The cut surface was dark red, moist, and friable and, when scraped with a knife, presented minute pockets of pus. The mucosa of the pharynx, trachea, and bronchi was a red gray, and the latter contained sanguinopurulent material. Microscopic examination of the left lower lobe revealed extensive hemolysis of red blood cells with only ghosts of cells remaining and numerous polymorphonuclear leucocytes dispersed among them. In some of these areas the lung architecture was entirely absent, and in the center of these, clumps of bacteria were present.

Two of the cases in which the pleural cavity contained no free fluid presented the following picture: In the first, there were few thin

fibrinous adhesions between the lung and pleura. The posterior portion of the lower lobes presented dark red, moist areas, and the cut surfaces presented small gray patches of consolidation. Microscopic examination showed that these small patches of consolidation were located about the terminal bronchi and bronchioles (Fig. 3).

The lumina of these and adjoining alveoli were completely filled with numerous polymorphonuclear leucocytes and few mononuclear cells. The alveolar septa were broadened, and their capillaries were distended. The epithelium of some of the bronchi was absent. The capillaries in their walls were distended, and the walls themselves contained polymorphonuclear leucocytes and small and large mononuclear cells.



Fig. 4.-Abscess with clumps of bacteria (X65).

In the other case the epiglottis, larynx, trachea, and bronchi were covered with a necrotic fibrinopurulent exudate. The mucosa of the larynx was ulcerated. The tracheal mucosa was necrotic, and this process extended into the mucous glands. The lungs were voluminous, and a fibrinous exudate was present over the posterior and diaphragmatic surfaces of the lower lobes. The lower lobes were firm and nodular. The cut surfaces presented brownish-red consolidated areas and minute abscesses.

Microscopic Examination.—There were numerous hemorrhagic areas, in which the alveolar walls were barely discernible and in which the red cells blended into a homogenous mass. Toward the center of the hemorrhagic zone, there was another zone made up of large monomuclear cells with few leucocytes. The alveolar walls were barely

recognizable. In the center there were clumps of bacteria surrounded by cells with pyknotic nuclei (Fig. 4). An adjoining artery showed numerous cells loaded with bacteria.

The remaining organs in this group presented nothing unusual, with the exception of the one infant, who also showed an interstitial hepatitis and fibrosis of the pancreas. Sections of these organs were carefully searched for spirochetes, but none were found.

Secondary Group.—In this group an entirely different picture presented itself at necropsy. In nearly all of them an osteomyelitis was present. Abscesses were found in many of the other organs as well as the lungs. They were present in the kidneys, myocardium, adrenals, pancreas, and voluntary striated muscles. In a few instances a purulent pericarditis was also present. In the lungs and kidneys the conglomerate miliary abscesses when seen on the surface of the organs appeared as "carbuncles."

#### DISCUSSION

The separation of our cases into two groups was based on clinical, bacteriologic, and pathologic differences. In the primary cases the history was chiefly that of an upper respiratory tract infection, with subsequent extension of the inflammatory process to the lungs. the secondary cases the history was that of a sepsis with the development of the pneumonia as an additional and often terminal incident. In the primary cases the physical findings were limited to the respiratory tract. In the secondary cases the clinical picture was dominated by the symptoms referable to primary and suppurative foci other than the lungs. In the patients with primary pneumonia blood cultures were sterile, or at most only evanescent bacterial invasions were demonstrable. In the secondary cases the blood stream invasion was heavy and persistent. The primary cases on autopsy showed pathology limited almost entirely to the lungs. Microscopic examination showed alveolar damage with no evidence of embolic phenomena in the blood vessels of the lung. In the secondary cases there was involvement not only in the lung, but throughout the body, and the pulmonary blood vessels showed widespread embolization. We have no evidence as to the pathogenesis of the disease in all our cases, but a study of the pathology seems to indicate that in the primary cases the portal of entry was bronchogenic. In most of the cases the lesions were almost entirely arranged about the terminal bronchi and bronchioles. In one instance a necrotic process extended from the epiglottis directly into the parenchyma of the lung. In another case, as illustrated in Fig. 2, a lipoid type of reaction was present, indicating aspiration of some foreign material.

We were interested in the significance of the bacteriemia in some of the primary cases. We feel that these small invasions of short

duration have the same relationship to primary staphylococcus pneumonia as the transitory early pneumococcemia has to pneumococcus pneumonia. It does not necessarily mean that the pneumonia was secondary to a sepsis.

The role of the staphylococcus organism in the primary cases calls for some comment. In the great influenza epidemics the staphylococcus was often found in the lungs at autopsy and was considered a secondary invader. Although we consider the staphylococcus as the essential etiological agent in our primary cases, the possibility of a virus having been the predisposing cause must also be considered. Many of our cases did resemble patients with acute influenza.

There were a few interesting facts brought out regarding staphylococcus infection. Secondary staphylococcus pneumonia followed the usual tendency of staphylococcus infection. Secondary staphylococcus pneumonia followed the usual tendency of staphylococcus infection to occur in the summer time, but primary staphylococcus invasion of the lung was much more frequent during the winter and early spring months So far as age was concerned, the primary cases occurred chiefly in patients under 1 year of age, whereas other types of staphylococcus infection are more prone to affect older children. Secondary staphylococcus pneumonia followed the same tendency as other forms of staphylococcus infections to predominate in the male, but the primary cases were equally distributed between both sexes. It was interesting to note that the mortality in staphylococcus sepsis with lung involvement is much higher than in staphylococcemia per The mortality of primary staphylococcus pneumonia on the other hand is only moderately higher than the general series of cases of staphylococcus sepsis.

The resemblances to, and the differences from, pneumococcus pneumonia were of great interest. The pathology of staphylococcus pneumonia resembles in many ways the pathology of staphylococcus infection elsewhere in the body. The pathogenesis is similar to that of pneumococcus pneumonia. The clinical picture in some particulars closely resembles, and in other ways is in distinct contrast to, the pneumococcus pneumonias.

The points of resemblance between primary staphylococcus pneumonia and primary pneumococcus pneumonia are as follows:

- 1 There is the same incidence of positive blood cultures.
- 2 There is the same distribution of cases in the winter and early spring months
- 3 There is the same relationship of upper respiratory infection and lung infection.
- 4 Many cases have the same type of fastigial temperature commonly associated with pneumococcus infection.
  - 5 Many cases have the same type of acute onset,

- 6. Most of the cases had the physical findings associated with a lobar distribution of the infection.
- 7. Most of the patients had definite, and often severe, associated upper respiratory infection.
  - 8. There were no distant pyogenic localizations.
- 9. The white counts varied from low to very high; the low counts were associated with a fatal prognosis.

The points of difference between primary staphylococcus pneumonia and primary pneumococcus pneumonia were:

- 1. The staphylococcus cases occurred predominantly below the age of one year.
- 2. The onset and course in staphylococcus cases were more often fulminating in a previously healthy child.
- 3. The onset in the course of a chronic illness could be so insidious that a diagnosis was made only after, or a short time before, death or during the last days of life.
- 4. Empyema occurred in more than three-fourths of the staphylococcus cases.
  - 5. Pyopneumothorax occurred in two cases.
- 6. The empyema fluid in about 20 per cent of the cases indicated there were destruction of tissue and bleeding into the pleural cavity.
- 7. In the staphylococcus cases there is a greater tendency for the occurrence of diarrhea and distention.
- 8. There is also a greater tendency toward the appearance of renal involvement.
- 9. The mortality in the staphylococcus pneumonia was 65 per cent: overwhelmingly greater than in the pneumococcus cases observed by us or reported by others.

#### SUMMARY

Thirty-seven eases of staphylococcus pneumonia are classified and the clinical features described. The pathology and bacteriology are described in different types of cases, and the pathogenesis is discussed. A summary of the differences from, and similarities to, pneumococcus pneumonia is given.

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## IRRADIATED EVAPORATED MILK AS A FOOD FOR INFANTS

A STUDY OF GROWTH, ELIMINATION, PROTECTION FROM RICKETS, AND MORBIDITY IN UPPER RESPIRATORY INFECTIONS IN COMPARATIVE GROUPS FED ON IRRADIATED AND NONIRRADIATED EVAPORATED MILK

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RRADIATED evaporated milk has been used extensively in the feeding of babies. It was the impression of one of us (H. N. S.) that babies fed this food were more likely to develop diarrhea than were infants on nonirradiated evaporated milk. While nothing on the subject has been published, so far as we know, there has been a rather widespread impression that this is true. At least, we have heard it from several different parts of the country. It seemed only fair, therefore, to make a comparative study of the two foods, namely, nonirradiated and irradiated evaporated milk, as thoroughly controlled as possible to determine whether this impression was justified.

In the course of this study in order to make a proper comparison, it was felt that we should also have a record of disease conditions, especially upper respiratory infections, and incidentally information on whether or not these children developed subclinical or clinical rickets. The infants studied came to the Welfare Station of the Central Free Dispensary, Chicago, which is a teaching center for the Rush Medical College. They live in the immediate neighborhood, which is a slum area. The babies selected were in good physical condition, and when the study started, all of them were under three months of age, most of them about six weeks old. They were followed until they were one year old; no baby is included in the study who was not under observation for at least three months. The study continued for two years so that the seasonal variation is not a matter of concern. We began in November, 1936, and continued until November, 1938, and a total of two hundred infants was observed.

The infants, as they were registered in the clinic, were placed alternately on feedings of irradiated and nonirradiated evaporated milk. The milk was bought in the open market and the labels removed. Milk was supplied weekly to the families in the quantity needed. Each child was fed 1 oz. of evaporated milk per pound body weight and 5 per cent carbohydrate in the form of cane sugar. The

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group fed nonirradiated evaporated milk was given in addition viosterol 100-D; in the beginning 10 drops a day and later 20 drops a day since in one instance 10 drops unfortunately failed to prevent the appearance of rickets in the roentgenograms. Cereal was added at four months, vegetables at five months, egg at six months, and a second cereal at eight months to the diets of all babies.

In the early part of the study, the nurse made a daily visit to each family to obtain the stool record. As the number of infants in the study increased, it became necessary to reduce the number of visits to one a week. However, between these visits the child was brought to the Station where a stool history was again taken. Thus a stool history was obtained every three or four days. In every instance where an increased number of stools was recorded, the nurse visited that child in the home daily and checked on the number of stools until the condition had improved. The same was true when respiratory infections were reported. The children were examined every two weeks by the physician in the Infant Welfare Clinic, where, besides the usual physical examination, the children were checked for signs of rickets. Roentgenograms of the long bones were taken at three-month intervals.

#### RESULTS

Of 103 infants who were given irradiated evaporated milk, 68 per cent were studied for one year. Of the 89 infants on nonirradiated evaporated milk, 70 per cent were studied for one year. The average number of stools per day for infants on irradiated evaporated milk was 2.0 and for those on nonirradiated evaporated milk 2.3. There were 144 upper respiratory infections during the entire period, or an average of 1.4 per infant in the group given irradiated evaporated milk, and 101, or an average of 1.1 per infant, in the group given nonirradiated evaporated milk. In the group given irradiated milk 36 of the infants had more than one cold and in the nonirradiated group, 24.

Inasmuch as two stools per day seemed to be about the average for both groups, it was decided to consider separately all infants having more than three stools per day for at least forty-eight hours. These cases were divided into two groups, (1) those in which the diarrhea was accompanied by respiratory infections and (2) those in which there was no such etiological factor evident.

In the group given irradiated evaporated milk there were 109 instances of babies having more than three stools per day for more than forty-eight hours. This is an average of 1.06 attacks per baby for the study period. Of these 109 instances, 28, or 25.7 per cent, were accompanied by upper respiratory infections, and 81, or 74.3 per cent, were not. In the group given nonirradiated evaporated milk there were \$4 cases of babies having more than three stools per

day for more than forty-eight hours. This is an average of 0.94 attacks per day for the study period. Of these 84 instances, 23, or 27.4 per cent, were accompanied by upper respiratory infections and 61, or 72.6 per cent, were not (Table I).

TABLE I

	INFANTS	PER DAY	ATTACKS OF HAN 3 STOOLS 7 FOR MORE 8 HR.	E NO. OF S. PER DURING PERIOD	UPPER	KS WITH RESPIRA- NFECTIONS	RESPIR	s WITH- UPPER ATORY CTION
TYPE OF FEEDING	NO. OF IN STUDIED	AVERAGE STOOLS P	NO. OF ATTA MORE THAN PER DAY FOI THAN 48 H	AVERAGE ATTACKS INFANT I	NO.	PER CENT	NO.	Per Cent
Irradiated evapora milk Non-		2.0	109	1.06	28	25.7	81	74.3
irradiat evapora milk		2.3	84	0.94	23	27.4	61	72.6

The incidence of these cases of increased stools was higher during the early months. This is true for both types of feeding. At the earliest age (1 month) the incidence of increased stools was greater in the nonirradiated group. Throughout the balance of the study, excepting in the sixth and ninth months, this ratio changed, and the irradiated group showed a somewhat higher incidence of increased stools. There were two infants in the irradiated group who were hospitalized for diarrhea which cleared up, however, without changing the type of feeding.

The only deaths in the group occurred in the nonirradiated milk group: three infants died, one each, of congenital syphilis, pneumonia, and leucemia. There were four cases of eczema in each group. The average gain in weight was 1.3 pounds per month in each group. In the group on irradiated milk no signs of rickets either clinical or roent-genographic were found, while four infants in the group given non-irradiated evaporated milk and viosterol showed slight signs of clinical rickets. This was confirmed in only one instance by x-ray.

#### DISCUSSION

These groups of infants in which alternate babies were given irradiated evaporated milk and nonirradiated evaporated milk, respectively, were followed for a period of two years. The seasons and age groups were similar, and the average number of stools per day was practically the same for both groups. In fact, those given the nonirradiated evaporated milk had a slightly higher average number of stools than those given the irradiated evaporated milk. We can assume, there-

fore, that in a carefully controlled study there is no greater frequency of stools in infants fed the one type of milk than the other.

It was true in this study that certain babies given nonirradiated evaporated milk showed a tendency during the early weeks toward an increased number of stools, while in later months the opposite was true. However, it must be understood that in no sense of the word is this increased number of stools to be considered pathologic and in ordinary practice the increase would probably be overlooked. It is true that two infants in this group were hospitalized for diarrhea, but two infants in a series of 192 babies is too small a number to be considered as any indication. Also it must be remembered that we were dealing with an economic group in which it is very hard to maintain a good sterile technique. In both groups there was a tendency for an increased number of stools in the younger infants.

The incidence of upper respiratory infection was high in both groups. It was higher in the group given irradiated evaporated milk than those given nonirradiated evaporated milk. For this we have no explanation. The nonirradiated evaporated milk group was given viosterol or vitamin D only, so that there was no advantage in the amount of vitamin  $\Lambda$  to either group. It had to be obtained from the milk in both cases.

We were particularly impressed with the absence of rickets in the group of infants given irradiated evaporated milk. It is often stated that certain babies cannot obtain enough protection from rickets on irradiated evaporated milk. Certainly when 103 infants raised under the social conditions of this district show no clinical or roentgenologic signs of rickets, it speaks well for the antirachitic qualities of irradiated evaporated milk. As stated at first, the babies given non-irradiated evaporated milk were given 10 drops of viosterol 100-D a day. In the very first roentgenograms taken one of these infants showed signs of rickets. The amount of viosterol was then increased to 20 drops a day. This resulted in control of this infant, and none in the future showed any signs of rickets by roentgenogram.

The frequency of infantile eczema was practically the same in each group as one would expect. Incidentally these eczemas were not as severe as are found in some breast-fed infants.

The gain in weight was exactly the same for each group.

#### SUMMARY

In a study carried on for two years with a group of infants given irradiated evaporated milk and nonirradiated evaporated milk and viosterol, the following facts were observed:

1. The average number of stools was practically the same for each group (2.0 per day for the irradiated milk group and 2.3 per day for the nonirradiated milk group).

- 2. In certain of the babies in both groups, there was a tendency occasionally to have more than three stools per day. This tendency occurred oftener in younger infants. It was slightly more marked during the first weeks in the nonirradiated milk group and during the later months in the irradiated group.
- 3. The average gain per month was the same in both groups (1.3 pounds per month).
- 4. None of the infants in the group given irradiated evaporated milk showed any signs of rickets either clinically or roentgenologically. Four infants in the group given nonirradiated evaporated milk and viosterol showed slight signs of clinical rickets, but of these only one showed signs of rickets by roentgenogram.

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## PREVENTION OF PURULENT OTITIS MEDIA IN INFANTS

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O TITIS media is more frequent in infancy than during any other period of life. It is usually secondary to nasopharyngeal infections, particularly rhinitis; pneumonia; the exanthemas, particularly scarlet fever and measles; and acute intestinal intoxication. Marriott¹ and others² believe it to be causally related to intestinal disturbances; and this viewpoint is probably responsible for many premature and unwarranted paracenteses.

The pediatrician and general practitioner, rather than the otologist, are generally the first to encounter this disease, and they are usually called upon to advise as to its proper management. They must, therefore, be well acquainted with the pathology, symptoms, and physical signs of otitic infections.

The middle ear and the mastoid sinus are extensions from the nasopharynx and communicate with it through the eustachian tube, a short canal which runs laterally, slightly upward, and backward from the nasopharynx to the anterior wall of the tympanum. In the infant the canal is about 15 mm. long, is straight and nearly horizontal, and has a lumen of adult proportions. Lymphoid tissue is found at the pharyngeal orifice in close proximity to the other lymphoid structures of the pharynx. A short, wide direct route is thus formed for the extension of infection from the nasopharynx to the middle ear.

Clinical observation over a period of years has led us to believe that myringotomy is practiced too freely in infants and that resolution of the exudate in the middle ear often follows conservative treatment. For the past five years (1934-1938) rigid criteria for incising the membrane have been set up on the Children's Medical Service at Bellevue Hospital, and myringotomy is performed only with the approval of an attending physician. The indications for myringotomy are complete obliteration of the landmarks, especially the short process, a bulging gray drum, together with fever, restlessness, and disturbed sleep. When the pain seems intense, together with great restlessness and loss of sleep, the above criteria may be modified.

Frequent examinations by the house staff are discouraged since the proximity necessary for the otoscopic examination exposes the infant to the expired air of the examiner thereby increasing the hazard of respiratory infection in the child. Furthermore, manipulation in the canal, by traumatizing an already inflamed drum, may aggravate the

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condition further. To minimize the danger of infecting the infant by the physician, all ear examinations are made with the infant lying on the abdomen, the head being turned away from the examiner. Physicians with respiratory infections are warned against making otoscopic examinations.

These observations were made on a ward for acute conditions for infants under 2 years, and the conclusions are therefore limited to this age group. A three-year period, 1931-1933, was used as a control. The term purulent of this media as here used means a purulent discharge from the ear.

Table I is a summary and includes data on which most of the charts and tables are based.

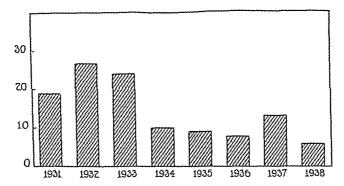


Chart 1.-The incidence of purulent otitis media in percentage of admissions.

Chart 1 illustrates the incidence of purulent otitis media, in percentage of all ward admissions, for the years 1931-1938. The dramatic drop after 1933 is evident. During the control period (1931-1933) 23.3 per cent of all patients admitted had purulent otitis whereas only 8.9 per cent suffered from this condition during 1934-1938, a reduction of 62 per cent.

TABLE I

THE INCIDENCE OF PURULENT OTITIS MEDIA FOLLOWING MYRINGOTOMY AND SPONTANEOUS RUPTURE AND THE INCIDENCE OF BILATERAL AND UNILATERAL OTITIS MEDIA

	NUMBER OF	NUMBER OF INFANTS WITH PURULENT OTITIS MEDIA			NUMBER OF INFANTS WITH	NUMBER OF INFANTS WITH	
YEAR	WARD ADMISSIONS	TOTAL	AFTER MYRIX- GOTOMY	SPON- TANEOUS RUPTURE	BILATERAL PURULENT	UNILATERAL PURULENT OTITIS MEDIA	
1931	996	189	127	62	121	68	
1932	842	227	146	81	154	1	
1933	766	190	132	58	116	73	
1931-1933	2604	606	405	201	391	74	
1934	725	72	28	44	35	215	
1935	752	62	29	33	25	37	
1936	780	55	27	28		37	
1937	693	90	53	37	30	25	
1938	644	42	21	21	48	42	
1984-1988	\$594	521	158	163	13	29	
			1 2000	1 200	151	170	

Chart 2 illustrates the incidence of bilateral and unilateral purulent otitis media. The more striking reduction in the occurrence of bilateral otitis is apparent. During the years 1931-1933 there were 1.8 times as many infants with bilateral purulent otitis as unilateral, whereas during 1934-1938 the number of unilateral cases exceeded the bilateral. This

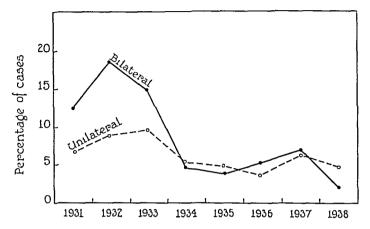


Chart 2 -The incidence of bilateral and unilateral purulent otitis media.

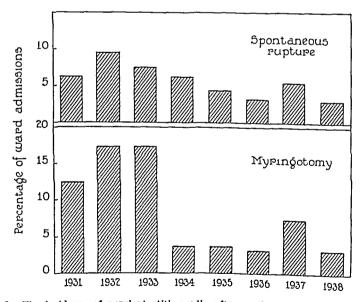


Chart 3.—The incidence of purulent offits media after myringotomy and spontaneous rupture.

means that, during the supervised period, there was not only a reduction in the number of infants with purulent of otitis media, but that, in contrast to the control period, bilateral of this media was no more frequent than unilateral.

In Chart 3 the incidence of purulent otitis media after myringotomy and after spontaneous rupture is compared. The reduction in purulent otitis media following myringotomy is striking (from 15.6 per cent of all ward admissions, 1931-1933, to 4.4 per cent, 1934-1938). There was also a fall in the cases following spontaneous rupture (from 7.7 per cent of all ward admissions, 1931-1933, to 4.5 per cent, 1934-1938). With conservative treatment one might have expected an increase rather than a decrease in this group. That this did not occur is probably dependent on a number of factors. Frequent examinations, particularly by the inexperienced, may lead to trauma of the already inflamed drum, thereby aggravating the otitic infection. Furthermore there is danger that

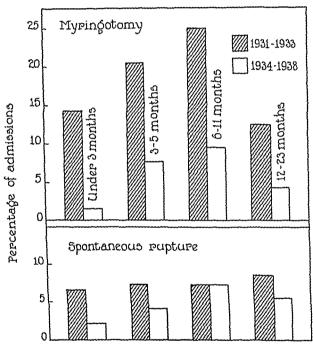


Chart 4.—The incidence of purulent otitis media by certain subdivisions of age under 2 years.

the infant's nasopharynx may be infected by the examiner; and this is naturally more likely to occur the more frequent are the examinations. Since otitis media is so often a complication of nasopharyngitis, this would lead to an increase in the incidence of otitis media. It has also been our impression that a diagnosis of spontaneous rupture is often erroneously made where a little moisture is seen on the drum.

In Chart 4 the annual incidence of otitis media, by certain subdivisions of age under 2 years, is compared for the two periods (1931-1933 and 1934-1938). The data for this chart were calculated in percentages of infants admitted in the various age groups. There has been a reduction in the occurrence of purulent otitis media in all age subdivisions. The fall was most striking in the age group under 3 months where purulent otitis media after myringotomy dropped from 14.4 to 1.8 per cent, and after spontaneous rupture from 6.7 to 1.8 per cent. Purulent otitis media is unusual in young infants, the total incidence under 3 months during the supervised period being only 3.5 per cent.

Tables II and III, respectively, show the incidence of purulent otitis media in pneumonia (all forms) and in diarrheal diseases. In both disease groups the incidence of purulent otitis media has been reduced to approximately one-third between 1931 and 1938. The data on diarrheal diseases are of particular interest since the belief still persists that many instances of intestinal intoxication are specifically related to middle ear infections.

TABLE II
THE INCIDENCE OF PURULENT OTITIS MEDIA IN INFANTS WITH PNEUMONIA (ALL. FORMS)

YEAR	NUMBER OF INFANTS WITH PNEUMONIA	NUMBER OF INFANTS WITH PURULENT OTITIS MEDIA	PERCENTAGE OF INFANTS WITH PURULENT OTITIS MEDIA
1931	111	39	35
1932	128	58	45
1933	141	36	26
1981-1988	380	133	35.0
1934	111	10	9
1935	92	9	10
1936	97	7	7
1937	73	22	30
1938	70	11	16
1984-1988	443	59	13.3

TABLE III
THE INCIDENCE OF PURULENT OTITIS MEDIA IN INFANTS WITH DIABRHEA

YEAR	NUMBER OF INFANTS WITH DIARRHEA	NUMBER OF INFANTS WITH PURULENT OTITIS MEDIA	PERCENTAGE OF INFANTS WITH PURULENT OTITIS MEDIA
1931	94	22	23
1932	78	36	46
1933	96	22	23
1981-1988	<i>868</i>	<i>80</i>	26.7
1934	60	8	13
1935	64	4	6
1936	75	2	š
1937	63	7	11
1938	81	5	6
1984-1988	545	26	7.6

In Table IV is shown the number of infants operated on for mastoiditis. The percentage of operative cases fell from 1.38 per cent of all admissions during 1931-1933 to 0.56 per cent during 1934-1938, a drop to less than half. Of the infants with purulent otitis media, the percentage operated on for mastoiditis during the two periods remained about the same (1931-1933, 5.9 per cent; 1934-1938, 6.2 per cent).

TABLE IV

THE INCIDENCE OF MASTOID DISEASE

YEAR	NUMBER OF ADMISSIONS	NUMBER OF INFANTS OPERATED FOR MASTOID DISEASE	PERCENTAGE OF ADMISSIONS OPERATED FOR MASTOID DISEAS	
1931	996	9	0.9	
1932	842	10	1.3	
1933	766	17	2.2	
1931-1933	2604	36	1.38	
1934	725	3	0.4	
	752	6	0.8	
1935	780	4	0.5	
1936	693	5	0.7	
1937	* -	2	0.3	
1938	644 <i>3594</i>	20	0.56	
1934-1938	0094 	~0		

#### DISCUSSION

These observations demonstrate that incising an inflamed drum often leads to a purulent discharge in an ear in which, if there were no operative interference, the infection would spontaneously subside. more, the results strongly indicate that frequent examinations of the ear, by traumatizing the drum and the canal and by exposing the nasopharynx of the infant to the expired air of the examiner, favor the development of purulent otitis media. It is of interest in this connection to quote the opinion of a prominent otologist3: "As a result of long observations, it has become evident that to incise the drum too early in the course of the development of an acute suppuration of the middle car is to add a factor toward the promotion, rather than toward the retardation of the middle ear infection." A similarly conservative view is voiced by Brennemann,4 who states that "the practical measure of bulging is the short process. So long as it is in evidence even as a tiny spot, there is rarely an indication for immediate paracentesis. When it is gone, the indication commonly exists but not always. An acutely bulging drum may subside spontaneously."

In many pediatric hospitals otitis media is treated casually and its management left to the house officers without adequate supervision by the visiting staff. This attitude is fraught with danger since it exposes children, already ill, to the danger and inconvenience of unnecessary paracenteses and purulent otitic discharges. Though mastoid disease is uncommon in infants, it does occur and is to be avoided if possible.

The data in the tables and charts show how, with eareful supervision, strict adherence to a standardized set of indications and avoidance of too frequent examinations, the incidence of purulent otitis media may be reduced and the danger of mastoid disease lessened.

The results of this study lend no support to the view that delay in incising an ear drum is harmful to the child. Where doubt exists,

we believe that it is preferable to wait. In acute intestinal intoxication, where a specific relationship to otitis media purulenta acuta has been hypothecated, the incidence of aural discharge has been reduced to onethird, with a fall rather than a rise in case fatality from this serious disease.

### SUMMARY AND CONCLUSIONS

During 1934-1938 the management of otitis media on the Children's Medical Service, Bellevue Hospital, has been carefully supervised and a strict set of indications for myringotomy set up. The incidence of purulent otitis media during this period was compared with that during a control period (1931-1933).

The incidence of purulent offitis media was reduced from 23.3 per cent of all admissions in 1931-1933 to 8.9 per cent of all admissions in 1934-1938.

Whereas, during the control period (1931-1933) 1.8 times as many infants had bilateral purulent otitis media as unilateral, during the supervised period (1934-1938) the number of unilateral cases actually exceeded the bilateral.

The incidence of purulent otitis media among the infants with diarrheal diseases and with pneumonia was reduced to less than one-third during the supervised period.

Operations for mastoid disease were reduced from 1.38 per cent of all ward admissions during the control period to 0.56 per cent during the supervised period.

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## REPEATED GLUCOSE TOLERANCE TESTS IN CHILDREN

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THIS study comprises repeated glucose tolerance tests on children in the first and the second decades. My object was mainly to see if the curve obtained at first examination remains unchanged or if it changes on repeated examinations, and if so, to determine the cause for these changes. These children had come to the Cleveland Clinic, for various reasons. A very brief case history summary is given at the end. The glucose load was 75 gm. up to 16 years of age, 100 gm. after that. The blood sugar levels were determined by the Myer modification of the Benedict method, using 1 c.c. of blood for each determination. Charts 1 to 19 are all constructed on the same scale so that comparisons can readily be made.

First, we have to consider the question of whether a glucose tolerance test curve is stabile or labile. Table I is an analysis of these curves. Ninety per cent of the curves which were normal at start remained normal, and one case, or 10 per cent, later became diabetic. Of those showing a diabetic curve at start, 55.5 per cent continued the same, and 4 cases, or 45.5 per cent, later became normal. The author is well aware of the fact that this is too small a series for a basis of any definite ex cathedra postulations, but it does offer us a

TABLE I

CHANGES IN THE GLUCOSE TOLERANCE CURVE WITH REPEATED TESTS

AT START	NUMBER CASES	CONTINUED SAME	PER CENT	BECAME DIABETIC	PER CENT	BECAME NORMAL	PER CENT
Children Normal Diabetic	10 9	9 5	90.0 55.5	1	10.0	4	45.5
Adults Normal Diabetic	56 71	45 50	80.3 70.4	11	19.6	21	29.6

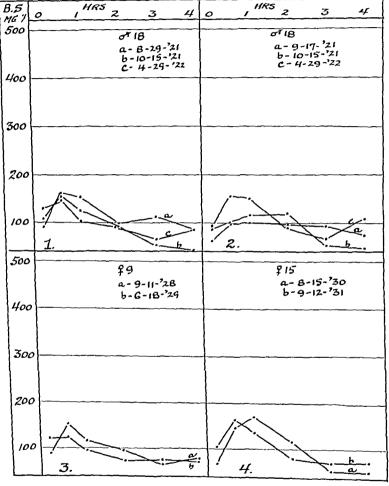
general lead. Similar studies on adults are included in the table for comparison. Here, as well as in the group of children, those who started out with normal curves and maintained them, the figures run fairly parallel. Where we meet with a deviation in these two groups is in the series starting with a diabetic curve. In the adults 29.6 per cent later turned normal against 45.5 per cent in the children. This fact would suggest that the curve in children is more labile than in the adults: that there are more factors, or else the factors which tend to disrupt temporarily the carbohydrate metabolism are more powerful, or more easily overbalanced than they are in later years. That these factors which tend to disrupt the carbohydrate metabolism are many can be seen from two lists following this paragraph. The problem of

endocrine disturbance plays a large part in some of these cases. Hypopituitary disease tends to give a low curve, and hyperpituitary disease gives a diabetic type of curve; hyperthyroidism, a high one; and hypothyroidism, a low one. A patient with hypothyroidism, given thyroid extract over a long period of time, may turn from a low normal curve to a frankly diabetic curve if the dosage of the thyroid extract has been excessive. What happens during the overmedication can well happen if the glands of internal secretion pass from a hypoactive to a hyperactive stage or vice versa. These factors must be taken into consideration in the evaluation of a glucose tolerance curve. A patient showing a diabetic curve, regardless of the cause, should be treated and watched until his carbohydrate metabolism has righted itself, as it will do in some cases. It is also true that some of the endocrine conditions which disturb the earbohydrate metabolism will right themselves even if we do nothing. This I have seen and shown in the cases of hyperthyroidism. The only question which can be raised here is: Taking two equal series of patients with disturbances of the carbohydrate metabolism due to endocrine causes, one treated and the other untreated, will the incidence of diabetes be the same in both series? This question I can answer by a positive "no." untreated series will show a much larger incidence of diabetes. It is for this reason that we cannot afford to disregard an off-tolerance curve until we have assured ourselves that the metabolism has returned to normal.

# Factors Which Tend to Show Improvement in the Glucose Tolerance Curve

- 1. Patient's going on a restricted diet; reduction of overweight.
- 2. Freak diet is likely to cause diabetic curve and return to a normal diet will show a normal curve.
- 3. Fear of diabetes if the test proper is likely to cause release of adrenalin into circulation increasing the blood sugar, and thus giving a false diabetic curve at the time, though on subsequent examinations curve will be normal.
- 4. Slow absorption of glucose from the stomach due to nausea which prolongs the absorption and lengthens the curve. If nausea is absent subsequently, tests may be normal. The characteristic dip in the curve between the first and second hour is the manifestation of this.
- 5. Performance of glucose tolerance test immediately before or after a major operation, when it is likely to show a distorted curve. Such tests should be avoided.
- 6. Any state of dehydration will show up a higher curve and will be therefore misleading.
- 7. Glucose tolerance test in prediabeties or diabetics toward the end of pregnancy will show an improvement.

- 8. A normal calorie diet, high in carbohydrates.
- 9. Thyroidectomy in cases of hyperthyroidism with disturbance of carbohydrate metabolism.
- 10. Possible periodic variation in the insulin output or the nervous mechanism involved.



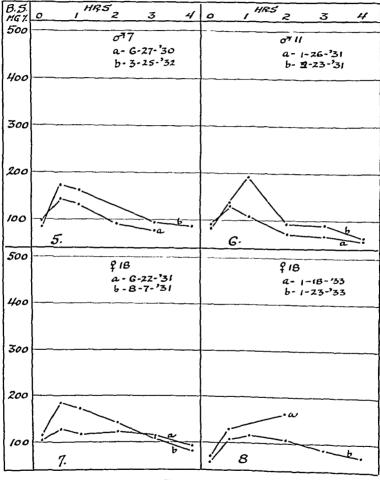
Charts 1-4.

- 11. The general or local increase in the alkalinity of an organism.
- 12. The use of alkalies (Underhill and Murlin).
- 13. Pyloric obstruction and vomiting.

Factors Which Tend to Make the Glucose Tolerance Curve Worse

- 1.  $\Delta$  patient who starts with a prediabetic curve and continues to overeat.
- 2. Infections, especially flu.
- 3. A gradual disintegration of the panereas from any cause.

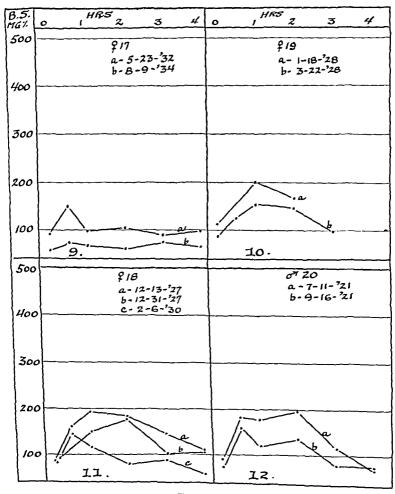
- 4. Any dieting preceding the test will give a false diabetic curve.
- 5. Diseases of the liver.
- 6. Hyperpituitary disease.
- 7. Hyperthyroidism in some cases.
- 8. Reaction following parturition, in mild diabetics or prediabetics.
- 9. Carbuncles.



Charts 5-8.

- 10. Obesity.
- 11. Anything stimulating the adrenals to overproduction of adrenalin.
- 12. Osteomyelitis and gangrene.
- 13. Partaking of acidifying diets thus causing slight acidosis.
- 14. Anemia.
- 15. Arterioselerosis.
- 16. Circulatory failure.
- 17. Emotional upheavals.

Does a normal curve indicate that the patient's insulogenic reserve is such that he is absolutely protected from the development of diabetes? Again I have to answer this question with a positive "no." It is rare, very rare, to see a normal curve later turn diabetic, but it does happen. Let us take the Curve 16, for instance, which in 1933 was a frank diabetic curve. The child was placed on a diet, and one and a half years later when the tolerance test was repeated the curve

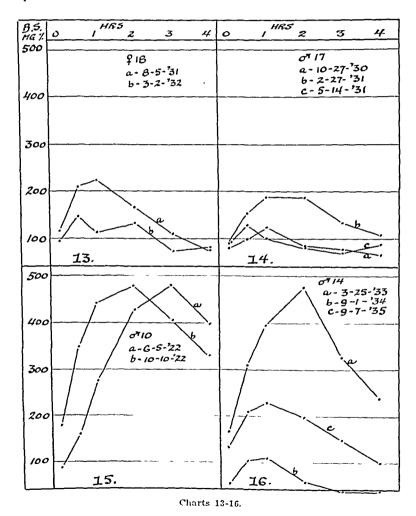


Charts 9-12.

was normal. He became careless, thinking he was cured, and ate everything. A year later a diabetic curve was the result. By this time enough damage was done to the pancreas that he was frankly diabetic and is now under treatment. Suppose a doctor had examined him in 1934 when he had a normal curve. He certainly would have thought that either an error occurred in 1933 or else the diagnosis of diabetes was a mistake. Only a prolonged observation would cor-

rect this opinion. It is for this reason that we teach "Once a diabetic, always a diabetic," even though there may be a marked improvement somewhere in the interim. Enough stress will break down this improvement in time.

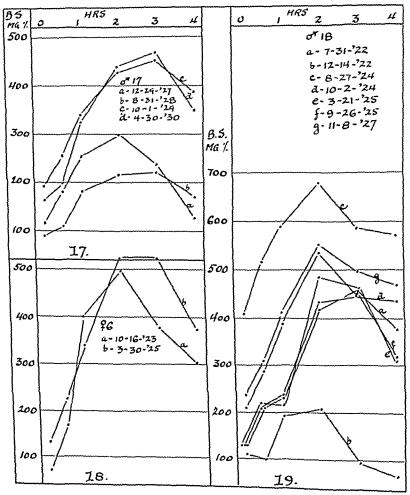
I think that we can consider the glucose tolerance test as a fairly stable phenomenon if care is taken and the test done under standard conditions. There can be a change in the curve in later years, just as changes occur in the function of other organs. The pancreas is no exception.



BRIEF CASE HISTORIES

- 1. Male, 18. In perfect health. Normal weight.
- 2. Male, 18. In perfect health. Normal weight.
- 3. Female, 9. Glycosuria. Weight -12 per cent. Treated as diabetic because of glycosuria for 2 months. Father diabetic. Paternal grandfather diabetic.

- Female, 15. Glycosuria. Weight minus 11 per cent. Blood sugar normal. Had glycosuria week ago. Losing weight. Paternal uncle diabetic.
- 5. Male, 7. Pituitary. Weight +20 per cent. Basal metabolic rate -23 per cent. Undescended testicle.
- Male, 11. Hypothyroid. Blood pressure 95/55. Weight -12 per cent. Basal metabolic rate -38 per cent.
- Female, 18. Blood pressure 152/90. Basal metabolic rate -18 per cent. Eye trouble. Drowsiness. Well developed and nourished. Improved on thyroid extract.



Charts 17-19.

- Female, 18. Simmond's disease. Weight -53 per cent. Basal metabolic rate -25 per cent. No menstrual periods. Patigue. Height 63.5 in. Hypogonadism.
- 9. Pemale, 17. Glycosuria. Blood pressure 112/74. Blood sugar normal. Weight -16 per cent. Large appetite. Menses regular.
- 10. Female, 19. Hypopituitary. Tendency to gain weight on low diet. Has not menstructed. Weight 140 pounds. Basal metabolic rate -26 per cent.

- 11. Female, 18. Petit mal. Adrenalectomy Dec. 23, 1927. Basal metabolic rate +7 per cent. Blood pressure 112/76. Weight -20 per cent.
- 12. Male, 20. In perfect health. Normal weight.
- 13. Female, 18. Pituitary dysfunction. Blood pressure 152/80. Obesity, weight +53 per cent. Basal metabolic rate -9 per cent.
- Male, 17. Pituitary. Basal metabolic rate 23 per cent. Right frontal craniotomy Feb. 16, 1931, with evacuation of suprasellar cyst. Blood pressure 110/40. Weight -17 per cent.
- 15. Male, 10. Diabetic 2 months.
- 16. Male, 14. Glycosuria. Weight +19 per cent. Tonsillectomy in 1924. On regulated diet. Glucose tolerance became normal. Relaxed routine, diabetes reappeared, and continued to date.
- 17. Male, 17. Glycosuria. Weight -15 per cent. This boy never did show hyper-glycemia on routine examination. Maternal grandfather diabetic.
- 18. Female, 6. Pneumonia in 1922, diabetes followed shortly after. Enlarged abdomen.
- 19. Male, 18. No diabetic history. Appendectomy in 1911. For a month classical symptoms of diabetes. Marked improvement in short time (see glucose tolerance, chart 2). Went to Europe, careless of routine, symptoms reappeared. Severe diabetic to this date.

# CEREBRAL VASCULAR LESIONS ACCOMPANYING SICKLE-CELL ANEMIA

J. M. ARENA, M.D. DURHAM, N. C.

ALTHOUGH the subject of sickle-cell anemia has been studied from many aspects, comparatively few reports are to be found on the manifestations of the disease as it affects the vascular system. Cook1 first published an account of neurological symptoms in a negro boy, aged 7 years, who had sickle-cell anemia. Evidence of a subarachnoid hemorrhage associated with cerebral softening was noted at autopsy. Cook apparently considered the conditions coincidental. Two negro children with sickle-cell anemia, who had had vascular accidents resembling those seen in adults, were reported from the Duke Hospital.<sup>2</sup> Both recovered except for a residual spastic hemiplegia. At that time the question was raised as to the possibility of both of these children having thrombi of the cerebral vessels due to the sickling of the red cells, similar to those which occur in the spleen. Cooley3 and Sydenstricker4 have seen similar vascular accidents in three patients with sickle-cell anemia. Ford<sup>5</sup> mentioned the fact that several negro children with thrombosis of the dural sinuses also had sickle-cell anemia, but he did not emphasize the significance of the sickle-cell anemia as a possible etiological factor. He reported the autopsy findings on a negro boy 18 months of age with sickle-cell anemia, who suddenly began vomiting, developed a diplegia, and died two days after the onset. Post-mortem examination revealed a thrombus in the superior longitudinal sinus with softening and hemorrhagic infiltration of the superior frontal and parietal lobes of the hemispheres. These changes extended almost to the fissure of Sylvius. There was also hemorrhage in the subarachnoid space over the superior and lateral surfaces of the brain which had spread to some extent into the basal cisterna. Kampmeier reported the case of a negro boy 10 years of age with sickle-cell anemia who had repeated attacks referable to the central nervous system, in the last of which there was hemiplegia. The patient recovered except for a residual spasticity on the right side. He emphasized the fact that pathologic changes characteristic of sickle-cell anemia permitted the diagnosis of cerebral thrombosis in his case. In a recent paper Yater and Hansmann7 presented further evidence that the vessels of the central nervous system may be involved in sickle-cell anemia. They reported the autopsy findings of a negress, aged 38 years, with sickle-cell anemia, who had

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hypertrophy and failure of the right side of the heart due to thrombotic occlusions of the small and medium-sized arteries of the lungs, but presented no neurological symptoms. However, sections of the brain showed blood in the meninges over the right hemisphere. A small area of softening about 1 cm, in diameter was found in the cortex in the left parietal region. The choroid plexus was uniformly shrunken and of ashen color, and in places appeared cordlike. Gross serial sections of the spinal cord revealed small petechiae in the nerve trunks as they emerged from the cord to enter the dorsal root ganglia These authors also felt that alin the dorsal and lumbar regions though 50 per cent of patients with sicklemia have enlarged hearts, there is usually something other than the severe anemia responsible for the cardiac failure, namely, hypertension of the lesser circulation due to numerous occlusions of the medium-sized and small pulmonary Harden<sup>8</sup> has described vascular changes in the retina as well as extremely tortuous and thickened superficial temporal vessels in two negro children with sickle-cell anemia.

We have seen the following five patients with sickle-cell anemia who have had vascular accidents. Autopsy in one of them substantiates the diagnosis and clarifies the relationship of the two existing conditions.

### CASE REPORTS

CASE 1.—A 6 year old negro boy entered Duke Hospital on Aug. 13, 1933, because of headache, dizziness, and unconsciousness. He had been well until two days before admission. At that time, he complained of stomachache, which disappeared after catharsis. The next morning his head ached, and shortly afterward he became dizzy and drowsy, and was too weak to climb into bed. His left arm and leg made spasmodic movements and his right limbs were powerless. Speech was only slightly impaired until later in the day, when he became stuporous. He had taken no food or water for twenty four hours preceding admission to the hospital. The family history was interesting in that a brother had died several months previously with a similar illness. A sister, aged 12 years, had had "rheumatism" for several years, and her blood smears showed 25 per cent immediate sickling. Smears of blood from the father and mother did not contain any sickle cells

Physical Examination—The boy's temperature on admission was 38° C. (100.5° F.); the pulse rate was 120; the respiratory rate was 28; and the blood pressure was 140 systolic and 75 diastolic. The patient was well developed, moderately dehydrated and in a semistuporous state. The skin was dry, and there was general glandular enlargement. The nail beds and mucous membranes were pale, while the sclerae were a deep greenish yellow. The tonsils had enlarged crypts and were moderately injected. There was a systolic murmur heard best at the apex and transmitted into the axilla. The right arm and leg were very weak and flaccid. The deep reflexes were hyperactive and the Babinski sign was present on both sides, but remained permanent only on the right side. The examination was otherwise negative.

Laboratory Tests—Hemoglobin, 98 gm. (64 per cent Sahli); red blood cells, 2,740,000; white blood cells, 17,450; polymorphonuclear leucocytes, 80 per cent; large lymphocytes, 8 per cent; small lymphocytes, 8 per cent, myclocytes and transitionals, 4 per cent. There was 25 per cent immediate sickling, and 75 per

cent within four hours. Bleeding time was one and one half minutes, and clotting time, one minute. Examinations of the stool and urine and intradermal tuberculin (0.1 mg. with old tuberculin), Wassermann and Schick tests gave negative results.

Course.—Immediately after the patient was admitted to the ward, a lumbar puncture was done and bloody fluid obtained. The spinal fluid was grossly clear the next day, but numerous red blood cells were found microscopically. The Pandy, tryptophan, and indole tests were negative. The patient remained in a semistupor ous condition, and the right arm and leg became spastic. Seven days after ad mission, a cisternal puncture revealed many crenated and sickled red blood cells in the spinal fluid. The patient gradually became less stuporous and more aware of his surroundings. Later he began to talk and improved steadily. However, three days before discharge (six days after admission) right facial weakness de veloped. The eye grounds remained normal. He returned to the dispensary at intervals of every few months and, except for residual spastic paralysis of the right side and right facial weakness, his general condition has been much im proved.

CASE 2.—J. G., a 6 year old negro boy, was first seen at Duke Hospital on May 26, 1936, because of paralysis of the right side, which occurred two days previously. Since the age of two years he had attacks of petit mal. The family and past histories were otherwise noncontributory.

Physical Examination—The temperature, pulse and respiration were normal. The blood pressure was 100 systolic and 60 diastolic. The boy was underdeveloped and poorly nourished. He had a papulopustular eruption over the trunk, legs, and arms. The mucous membranes were pale. The teeth were dirty and carious. The tonsils were enlarged, and the pharynx was reddened. The heart was enlarged, and a blowing systolic murmur could be heard over the entire precordium. The spleen was palpable. Neurological examination revealed weakness of the right arm and leg, right facial weakness, deviation of the tongue to the right, hyperactive deep reflexes, and a positive Babinski reflex on the right. There was no sensory impairment.

Laboratory Tests—Hemoglobin S.2 gm. (53 per cent Sahli); red blood cells 2,200,000; white blood cells, 16,150 with 76 per cent polymorphonuclear neutrophiles. Fresh preparation of blood revealed 90 per cent sickling of the red blood cells in 24 hours. The urine, tuberculin, Wassermann and Schick tests were negative.

Course.—The patient was given a high vitamin and high caloric diet. Five transfusions were given in the course of nine days and his hemoglobin rose to 10.8 gm. (70 per cent). Except for the residual spasticity and facial weakness on the right he was much improved.

CASE 3—R. L, a negro boy 10 years of age, was seen with Dr. C W. Purcell (Danville, Va). At the age of 6 years he had a vascular accident that left him with paralysis of the right side. His past and family histories were essentially negative. On physical examination he was found to be undernourished, weighing only 215 kg. (54 pounds). The anterior cervical glands were enlarged. The liver and spleen were two fingerbreadths below the costal margin. He had definite nystagmus in all directions. The fundi were pale; no exudate was seen. The deep reflexes on the right were hyperactive, and the Babinski was positive. He had sustained ankle clonus on the right.

Laboratory Tests—Hemoglobin 7.8 gm. (50 per cent Sahh). The red blood cells numbered 3,390,000, 90 per cent of which assumed the sickle form by the end of four hours. The blood and spinal fluid Wassermann tests were negative.

Course—Since the onset of hemiplegia he had been given iron and liver by mouth, but his hemoglobin has never been higher than 7.8 gm (50 per cent). There has been only slight improvement of his residual paralysis

CASE 4—D M, a negro boy, aged 4 years, was admitted to Duke Hospital on Dec 29, 1937, because of paralysis of the right side of three weeks' duration. He had a sudden onset of headache and vomiting Dec 7, 1937. At about the same time the mother noticed that he had weakness of the entire right side. He also had difficulty in swallowing, chewing and talking.

Physical Examination —The temperature, pulse, respirations, and blood pressure were normal. The patient was well developed and nourished, alert, and cooperative. Over his entire body were discrete scars. The eye grounds were normal. The lungs were clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. The spleen was palpable at the costal margin. Neuro logical examination showed almost complete spastic paralysis on the right and right facial weakness. The deep reflexes on the right were hyperactive accompanied by a positive Babinshi.

Laboratory Tests—Hemoglobin, 111 gm (72 per cent Sahli); red blood cells, 3,920,000, white blood cells, 8,000 with a normal differential count. The examina tion of the stool and urine and intradermal tuberculin (01 mg with old tuber culin) and Wassermann and Schick tests were negative

Course—The initial sickle cell preparation on this child was negative. How ever, on the third hospital day the temperature rose to 383°C (101°F) and another preparation at this time showed 100 per cent sickling. Splenectomy was advised, but the parents refused permission for the operation. There has been no improvement in the anemia or degree of spatienty.

CASE 5—A 4 year old negro girl first entered Duke Hospital on Feb. 8, 1934, with a history of paralysis of three weeks' duration. At the onset the child suddenly became speechless, her mouth drooped and saliva drooled from it. Two weeks later the child lost the use of her right arm and leg. The family history was interesting in that three other siblings died with a similar condition. In one of these siblings sickle cell anemia had been diagnosed in our clinic. This child died at home after having been followed in the Duke Hospital Clinic.

Physical Examination — Temperature, 37.5° C (99.5° F), pulse, 100, respiration, 28, blood pressure, 105/65. The child could neither walk nor speak but could comprehend commands and questions. The tongue could not be protruded nor moved from side to side. The spleen was pulpable 2 to 3 fingerbreadths be low the costal margin. Paralysis, weakness, and spisticity of right arm and leg were present. Reflexes were hyperactive throughout, but more marked on the right side. Babinski, Kernig and Brudzinski reflexes were negative. The spinal fluid was normal.

Laboratory Tests—A fresh blood smear showed 100 per cent sickling in four hours, hemoglobin was 78 gm (52 per cent Sahli), white blood cells, 24,000. An indirect van den Bergh reaction was present (trace). The patient was discharged with a diagnosis of sickle cell anemia with cerebral thrombosis in region of the left internal cipsule.

In an interval of three and one half years, during which time the patient was followed in the dispensary, the use of the right arm and leg returned, and speech improved almost to normal, however, finer movements with her right hand, such as writing, buttoning clothes, or holding table silver, could not be performed. A residual hmp and dragging of the right leg persisted

Three and one half veirs after the first admission the patient was again admitted to the hospital. Fifteen hours previously the child suddenly covered the frontal region of her head with her left hand and cried out that her head hurt:

she immediately crumpled to the floor. Her respirations were labored. Both legs were paralyzed, and she was unable to speak.

Physical Examination.—Temperature 39° C. (102.2° F.); pulse, 120; respiration, 38; blood pressure, 150/100. A small, undernourished 8-year-old negro girl lay unconscious in bed with mouth and eyes open, breathing rapidly and irregularly. The lungs were clear. A soft, blowing systolic murmur was heard over the entire precordium but best over the mitral area. The eyes moved aimlessly at times but tended towards left horizontal deviation. The spleen was not palpable. Both arms were spastic, more so on the right. The left leg was relaxed. Supraorbital pressure caused purposeful movements with both arms in an attempt to knock away the examiner's hands, and the left leg became spastic. Tendon reflexes were hyperactive on both sides, more marked on the right. The abdominal reflexes were absent; Kernig and Babinski, positive bilaterally. Response to pain stimuli was present over the entire body.

Accessory Clinical Findings.—Hemoglobin, 6.7 gm. (40 per cent Sahli); red blood cells, 1,500,000; white blood cells, 50,000; polymorphonuclear leucocytes, 94 per cent. Sickling, 25 per cent immediately; 95 per cent in 24 hours. The urine showed a four-plus albumin and from 5 to 10 granular and cellular casts per high power field. Spinal fluid showed initial pressure 270 mm., bloody fluid, slight xanthochromia, and 30,000 red blood cells. The Wassermann and colloidal mastic tests were negative. The patient was restrained, placed in a dark room, and given sedation and an infusion of 2.5 per cent glucose. No change followed, and she expired quietly 15 hours later with a temperature of 41° C. (105.8° F.).

Necropsy.—The large subarachnoid cerebral arteries were found to have undergone a gradual obliteration with final complete closure through a pathologic process identical with that which results in occlusion of the splenic arteries. The spleen which was so markedly enlarged on the child's first admission was a fibrotic nodular mass weighing only 1.5 gm. The complete autopsy findings are being reported in detail.9

### COMMENT

Thrombotic phenomena are important episodes in the life history of these patients, and obliterative vascular changes and thrombi are a part of the pathologic picture of sickle-cell anemia. The cause of the tendency to capillary engorgement and arterial thromboses is not definitely known. Diggs'10 theory that the distorted shape of the red blood cells prevents their ready passage through the capillaries probably explains the general vascular stasis, which is aided perhaps by the tendency of these cells to agglutinate. The amount of sickling seen in fresh blood preparations does not represent the actual amount of sickling present in the circulating blood, since the oxygen content of the air tends to restore the shape of the erythrocytes. It has been observed11, 12 that the degree of oxygen unsaturation plays a large role in the amount of sickling in vivo. However, further observations fail to correlate the relationship between the degree of anoxemia and the severity of the disease. 13, 14 There is also the possibility of an increase in the degree of capillary stasis and other factors such as fever and infections. In Case 4 although we suspected sickle-cell auemia, fresh smears failed to show the sickling until the patient's temperature rose to 38.3° C. (101° F.), at which time 100 per cent sickling was found. Recently we have had the opportunity of following a 9-month-old negro male with sickle-cell anemia and lobular pneumonia. At the height of his fever of 40° C. (104° F.) he had 50 per cent sickling within four hours. Two days after his crisis, while his temperature was normal, only 5 per cent sickling could be obtained in the four-hour period. Although the sickle-cell trait is said to exist in about 5 to 10 per cent of normal healthy negroes without anemia, and, although this condition has never been known to develop into sickle-cell anemia, still one might assume that in the presence of infection and fever some acceleration of the powers of sickling with anemia may take place.

In considering the pathologic findings in the fifth case one finds the changes in the splenic and cerebral vessels to be quite similar.

Our five patients were between the ages of 4 and 10 years. Four of them were males. The spleen was definitely palpable in four of the five patients. In Case 5, although the spleen was readily palpable at the time of the first vascular accident, three and one-half years later, when the second accident occurred, it could not be felt. Obviously considerable destruction of splenic tissue had taken place during the interval between the cerebral attacks. Although the results from splenectomy in these patients are not at all favorable in the several reported cases in the literature, the removal of an enlarged spleen gives better results than the removal of a small one.<sup>15</sup>

Recently Bosselman and Kraines<sup>16</sup> reported the case of a 13-yearold negro boy with sickle-cell anemia who developed aphasia six years after he had had a splenectomy. They suggested the occurrence of multiple small cerebral hemorrhages as the most likely cause of the symptoms. Apparently splenectomy in this particular patient did not prevent a vascular lesion. Nevertheless, certain patients with sickle-cell anemia show constitutional symptoms which are not unlike those seen with other true hemolytic anemias, namely, hemolytic icterus and erythroblastic anemia. Cardiac hypertrophy and dilation are the result of the recurring anemia or thrombotic phenomena,7 and we have seen marked retardation of skeletal growth in some of these children with sicklemia. Splenectomy has given dramatic results in correcting the deranged metabolism which interferes with skeletal growth and proper bone structure, especially in patients with congenital hemolytic icterus. Therefore, it would appear that splenectomy should be performed more often in children with sickle-cell anemia who have enlarged spleens and who show such marked constitutional symptoms.

### SUMMARY AND CONCLUSIONS

In the course of a study of five cases of sickle-cell anemia it has been shown that sickle-cell anemia may first become manifest as a disease through the appearance of signs and symptoms indicative of cerebral vascular disease. The clinical features in such cases lead to the diagnosis of either cerebral vascular thrombosis or intracranial hemorrhages.

The pathologic findings in one of the patients here studied establish the fact that in sickle-cell anemia the large subarachnoid cerebral arteries become occluded in much the same manner as the splenic vessels.

Capillary stasis due to distortion and agglutination of red blood cells and other factors such as fever and infections probably contribute to the tendency to capillary engorgement and arterial thromboses.

The removal of a large spleen in a child with a previous vascular accident and constitutional symptoms should be given a further trial.

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## TUBERCULIN PATCH TEST

A Comparison With the Pirquet and Mantoux Tests Samuel B. Weiner, M.D., and Adolph Neustadt, M.D. New York, N. Y.

THE tuberculin patch test was introduced in a commercially available form, in 1937 by Vollmer and Goldberger. They reported a high degree of skin sensitivity of this test in a group of tuberculous children. In 1938 these authors further reported on the close agreement of the patch test with the Pirquet test. Steward also reported a very high degree of agreement with the Pirquet test in tuberculous children.

Because of the relatively high incidence of tuberculous infection among colored children, we believed that the Pediatric Service of the Harlem Hospital would be a suitable place to study the routine applicability of the patch test.

### MATERIAL AND METHOD

Patch tests were done on 257 children. No attempt at selection of cases was made. The population represented is largely an indigent group, over 90 per cent of whom are negro.

The patch test was applied in the manner described by Vollmer. Simultaneously the Pirquet test was done with old tuberculin (Department of Health of the City of New York). The patch test was removed in two days. On the third day both the Pirquet test and the patch test were read. If both tests were negative or if the two tests did not correspond, a Mantoux test was done with 0.1 c.c. of a 1:1,000 solution of old tuberculin (Department of Health of the City of New York). As one might expect, it was not possible to do the Mantoux test in all ambulatory patients because of parental objections and failure to return after the Mantoux test was made.

#### RESULTS

In 200 cases both the patch test and the Pirquet test were negative. In 44 cases both tests were positive. The degree of reactivity was usually identical, but in 10 cases a marked difference was noted. In

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<sup>•</sup>The patch tests were made available through the Lederle Laboratories Inc., New York, N. Y. These patch tests were of a weaker strength (about 50%) than those at present distributed by the company.

6 of these the Pirquet reaction was stronger. In the other 4 the patch reaction was more marked. In 13 cases there was disagreement between the patch test and the Pirquet test (Table I).

Table I

RESULTS OF PATCH, PIRQUET, AND 1:1000 MANTOUX TESTS IN 257 CHILDREN

			MANTOUX 1:1000			
		CASES	NEGATIVE	POSITIVE		
Patch 0 Patch + Patch + Patch 0	Pirquet 0 Pirquet + Pirquet 0 Pirquet +	200 44 10 3	60 Not 2†	3 done 7* 1*		
		257				

\*Chest X-ray positive in 1 additional case in which Mantoux test was not done. †No clinical evidence of tuberculosis. Chest X-ray negative in one case.

The Mantoux test was done in 63 children in whom both the patch test and the Pirquet test were negative. The Mantoux test was negative in 60 children and positive in 3 children. Although the number of cases is small, we may conclude that the patch test showed about 95 per cent as many reactors as the 1:1,000 Mantoux test. Only 3 positive reactors were missed by the patch test.

In 10 patients the patch test was positive and the Pirquet was negative. The Mantoux test was positive in 7 of these cases and negative in 2. In one additional child the Mantoux test was not done because the chest roentgenogram showed a tuberculous lesion. There was no clinical evidence of tuberculosis in the 2 children with negative Mantoux tests. The chest roentgenogram in one child was also negative. The patch test was therefore more sensitive in 8 cases than the Pirquet test, whereas in 2 cases the patch test gave a false positive reaction.

The patch test was negative in 3 children who had positive Pirquet tests. The Mantoux test was positive in 1 of these children. In the second child the chest roentgenogram showed evidence of a tuberculous infection, and the Mantoux test was omitted. The third child did not return after the Mantoux test was done.

No general reactions were noted following any of these tests, nor were any of the skin reactions very severe. We found no difficulty in interpreting the patch test especially after some experience with it. Of the three tuberculin tests, the patch test is considerably simpler to do. There is a further factor that no pain is caused, and no "needles" are exhibited. A disadvantage to be reckoned with in young children is their tendency to remove the patch.

## CONCLUSIONS

It seems that the patch test is about as satisfactory as the Pirquet test in routine tuberculin testing.

From our series one would judge that 95 per cent of the positive reactors are determined by the patch test as compared to the 0.1 mg. Mantoux test. Two children gave positive patch tests without evidence of pulmonary tuberculosis. These children had negative Mantoux tests. It is our impression that these were false positive patch reactions. With this reservation in mind we believe that the patch test is a satisfactory tuberculin test for general use.

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## ATROPINE INTOXICATION

## ITS MANIFUSTATIONS IN INFANTS AND CHILDREN

HENRY G. MORTON, M D. DURHAM, N. C.

PERHAPS no other drugs, except phenobarbital, are more widely used in pediatrics than belladonna and its derivatives. They are used for the treatment of enuresis, pylorospasm, refraction of the eye or treatment of various eye diseases, preoperatively to diminish secretion, for the treatment of the chronic postencephalitic Parkinsonian syndrome, and many other conditions. Although atropine usually is used with impunity, symptoms of intoxication occasionally occur. Unfortunately they are often unrecognized as being related to the administration of the drug, and fatalities may result. From 1930 to 1938 eight cases of atropine poisoning with two fatalities have occurred among 3,200 pediatric admissions at the Duke Hospital. Because of the unusual features of some of these cases they are reported in detail.

#### CASES

Case I—M H, a 3 year old white girl, was brought to the Duke Hospital because she had perforated the cornea with a pair of scissors. Prior to operation, 6 drops of a I per cent atropine solution were dropped into the eye, and 0 1 mg. of atropine was given subcutaneously. After the operation (conjunctival flap for corneal perforation) approximately 15 gm of a 1 per cent atropine ointment were placed on the dressing next to the eye, and the child was sent to the ward at 11:20 p.m.

Laboratory examination showed the white blood count, 32,000, red blood count, 5,770,000, hemoglobin, 17 gm (110 per cent Sahli); urine, one plus albumin.

## Course

- 11 20 P.M Returned to the ward; pulse 134, respiration 24, color good.
- 11 40 PM Temperature 39 8° C. (103 7° F)
- 12.00 midnight Restless, thirsty, and complaining of heat; pulse 160, respiration 20
  - 2 00 A.M Restless, respiration shallow and rapid, respiration 54, pulse 168.
  - 4 00 AM. Vomited, slight flush, temperature 42° C. (107.6° F.).
  - 6 00 AM Voided and lind stool, nauseated; temperature 42° C. (107.6° F.), pulse 160, respiration 58
  - 8 00 vm Voided and had stool, vomited, body rigid, 03 gm aspirin and alcohol sponge given, temperature 41 8° C, fell to 40 8° C. (107.2 to 105 5° F).
  - 10 00 vm Eight ce 10 per cent calcium gluconate intravenously and a con tinuous siline subcutaneous infusion given; temperature 37.8° C. (100° F.)
  - 11 00 AM Vomited, responded poorly, 6 mg. pilocarpine given subcutaneously; pulse weak, temperature 38 5° C. (101 3° F.).

From the Department of Pediatrics, Duke University School of Medicine, and Duke Hospital

12:30 P.M. Two hundred c.c. 10 per cent glucose given intravenously; temperature 39° C. (102.2° F.).

1:00 P.M. Respiration labored, pulse weak and irregular, condition very poor, vomited, chewing tongue, alcohol sponge given. Temperature 40.3° C. (104.5° F.).

2:00 P.M. Green watery stool, ice packs applied.

6:12 P.M. Expired.

Total amount of atropine administered was 18.1 mg.

Post-mortem examination revealed perforation of the anterior chamber of left eye covered by conjunctival flap; acute congestion of the posterior portion of left upper lobe of lung; cloudy swelling of liver and kidneys; injection of superficial blood vessels of brain.

Case 2.—A 2-year-old negro boy was brought to the Duke Hospital because of a lye stricture of the mouth upon which a plastic operation had been done at another hospital. The morning of the operation, the patient was given atropine and morphine preoperatively, and atropine postoperatively in unknown amounts. About four hours after the operation the child had definite signs of pulmonary congestion and cardiac dilatation; he was transferred to Duke Hospital. At this time the temperature was 40° C. (104° F.); pulse, 180; respirations, 60; and blood pressure, 90/00. The child was dehydrated, and the skin was hot, dry, and loose over the abdomen. The pupils were contracted; the mouth showed signs of the repair operation; and the lips were dried and fissured. Respirations were rapid, and squeaks, wheezes, and râles were heard over both lungs. The heart was markedly enlarged to the left. No murmurs were heard. The abdomen was soft though slightly protuberant.

Laboratory examination showed white blood count, 14,000; hemoglobin, 14.4 gm. (93 per cent Saldi).

Course.—The child was placed in an oxygen box, and parenteral fluids were given. The temperature fell to normal, and the pulse to 120 by the next day. Within forty-eight hours the respirations fell to 40, sweating started, and by the third hospital day the heart had returned to normal size. The remainder of the stay was uneventful.

Case 3.—D. J., a 3-year-old white girl, was brought to the Duke Hospital because of failure to develop. The past history and physical examination revealed that the child had never walked or talked, was mentally deficient, and probably had a patent ductus arteriosus.

Laboratory examination showed white blood cells, 15,000; red blood cells, 4,750,000; hemoglobin, 15.3 gm. (98 per cent Sahli); urine and Wassermann test were negative.

Course.—The pupils were dilated with 2 drops of 1 per cent atropine in each eye for ophthalmoscopic examination. At 8 p.m. the temperature was 37.1° C. (98.7°F.). At 12 midnight it had risen to 39.3° C. (102.7° F.), and the child became very restless. At 4 a.m. the temperature was 40.1° C. (104.1° F.), and the patient began to shrick and had a generalized convulsion. Respirations became very irregular and labored; the heart became weaker; and at 7 a.m. the pulse was barely perceptible. The child died shortly thereafter despite the use of caffeine and adrenalin. The total amount of atropine administered was 2 mg. (2 drops of a 1 per cent solution in each eye).

CASE 4.—K. M., an 8-month-old white boy, was brought to the Duke Hospital because of inability to hold his head up, failure to gain weight, and vomiting. The referring pediatrist reported that when given 0.064 mg. (gr. 1/1,000) atropine every three hours for the vomiting, the child developed a high fever after two or three doses.

Laboratory.—Red blood count was 3,760,000; hemoglobin, 11.2 gm. (72 per cent Sahli).

Course.—The patient's temperature on admission was 37.2° C. (98.9° F.). The child was given 90 c.c. of formula every four hours with 4 drops of a 1 to 5,000 solution of atropine sulfate (0.04 mg.) twenty minutes before each meal. The temperature rose to 38.5° C. (101.3° F.) at 4 A.M., 39.5° C. (103.1° F.) at 4 P.M., and ranged there for the next two days. During this stage the pupils dilated, and the face was flushed. Atropine was discontinued on the third hospital day, and the temperature fell to 38° C. (100.4° F.) twenty-four hours later, and to normal within another twenty-four hours. The remainder of the hospital stay was uneventful.

Cases 5 and 6.—A. S. H. and M. M. H., white twins, are three alophen pills shortly before lunch; about one-half hour later the children looked flushed, and the empty pill box was found. The children were then brought to the Duke Hospital, and their stomachs were washed out. The only symptoms were flushed skin and dilated pupils.

Alophen pills								
Aloin	1/4	grain	16.0 mg.					
Strychnine	1/80	grain	0.8 mg.					
Belladonna	1/12	grain	5.0 mg.	(or	0.05	mg.	$\mathbf{of}$	atropine)
Ipecac	1/15	grain	4.0 mg.					
Phenolphthalein	1/2	grain	32.0 mg.					

Case 7.—R. D., a 5-year-old white boy, soon after receiving atropine drops for refraction, had a reaction. The temperature rose to 38.6° C. (101.4° F.), the skin became flushed, and he became hyperactive. The child was put to bed, ice packs were placed on the head. During the next two hours, the temperature returned to normal, the flush disappeared, and he made an uneventful recovery.

Cases 8 and 9.—A 4-year-old negro girl and her 2-year-old brother were given a broth made from jimson weed, which contains stramonium, the action of which is similar to that of atropine. Five hours later the children were brought to the Duke Hospital because they were stuporous and complaining of dizzy sensations. The temperature, pulse, and respirations were normal; the pupils were dilated and reacted poorly to light. A flush could not be seen. The children were screaming and irritable. The patients' stomachs were washed out, and fluids were "forced." Recovery was uneventful.

## SOURCE OF ATROPINE

Belladonna, its refined extracts, and related drugs are derived from plants, several of which grow wild in fields and, when ingested, contain a sufficient amount of the drug to cause poisoning. In some instances death has resulted from eating them.<sup>1</sup>

Atropa belladonna	The "deadly nightshade," found in cultivation.
Datura stramonium	"Thorn apple," "Jamestown weed," "jimson weed," or "cocklebur," found generally throughout the United States.
Hyoscyanus niger	"Henbane," found in northern United States, rarely in the South.
Mandragora officinale	"Mandrake," found in cultivation.

Poisoning has occurred from eating cooked turkeys<sup>2</sup> and rabbits,<sup>3</sup> which apparently had been feeding on some of the above plants. The serum of rabbits has been shown to neutralize atropine,<sup>4</sup> and this may account for the apparently normal condition of the animals. In one instance fifteen girls had mild toxic symptoms from eating Thanksgiving turkey; a broth from the meat of the fowl later readily dilated the pupil of an adult.<sup>2</sup>

The most common source of poisoning comes from the use of 1 per cent ophthalmic drops (1 drop containing 0.5 mg. or  $\frac{1}{120}$  grain). Poisoning has occurred in infants from the use of 2 drops of 1:1,000 solution (0.1 mg. [ $\frac{1}{600}$  gr.] to the drop) of atropine sulfate.<sup>5</sup> Poisoning has also occurred from the use of the drug when given subcutaneously.

## ACTION OF ATROPINE

In general the drug paralyzes the parasympathetic nerve endings and is antagonistic to the parasympathetic drugs. In small doses it stimulates and in large doses depresses all body functions. It speeds up respiration, reduces and may stop bronchial and other secretions, increases body temperature, produces a flushed skin, dilates the pupils, paralyzes accommodation, relaxes the intestines, and prevents overaction of the bladder muscles.

Amounts		Action
Mg.	Gr.6	
0.5	(1/120)	Slowness of pulse and very slight dryness of throat.
0.5 to 1	(1/120 to 1/60)	Dryness in mouth, often with thirst.
2	(1/30)	Pupils dilated, not quite immobile, increase of pulse rate.
3 to 5	(1/20 to 1/12)	Headache, dysphagia, alteration of voice, mus- cular weakness, and restlessness.
7	(1/10)	Considerable dilatation of the pupils, disturbance of vision.
8	(1/8)	Excitement and muscular incoordination more marked.
10	(1/6)	Apathy. Hallucinations of delirium; uncon- sciousness.

The figures above indicate the usual amounts which affect adults, except those who are hypersensitive to the use of atropine. The minimal lethal dose has been stated to vary from 80 to 130 mg. in adults, and around 10 to 20 mg. in children. Pilcher gave 2 to 6 mg. of atropine to eight children, varying in age from 1 to 3 years, half of whom were feeble-minded, without causing toxic effects. Despite these figures, deaths have been reported in adults from the use of 2 mg., and in children from the use of 0.4 mg. of the drug. The marked variation is well demonstrated by one child's ability to tolerate 16 mg. a day and another's reaction to 1 drop (0.05 mg.) of this same solution.

The usual atropine sulfate solutions used are 0.5 and 1 per cent; in the former one drop contains 0.25 mg. ( $\frac{1}{250}$  gr.) and in the latter

one drop contains 0.5 mg. (1/120 gr.) of atropine. Obviously the careless use of eyedrops may cause severe toxic manifestations in certain individuals.

## TOXIC SYMPTOMS

"Hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hen," describes the more common reactions seen in poisoning due to belladonna and its derivatives. Other reactions occur, however, with sufficient frequency to call attention to them. Dryness, thirst, flushing, dilatation of the pupils, and impairment of vision are usually the presenting symptoms, followed by a burning sensation in the throat, difficult swallowing, nausea, sometimes vomiting, excitement, delirium, visual hallucinations, staggering gait, rapid pulse and respirations, retention of urine (atropine is eliminated principally through the urine), diarrhea, numbness of the extremities, depression, coma, and death. A leucocytosis of 12,000 to 17,000 often is present. 5-9 The onset may occur within ten minutes after taking the drug. 10 or as late as a month after its continued use. 11 Fever, which occurs in about 10 per cent of children, has been unsatisfactorily explained, e.g., stimulation of the heat centers, suppression of sweating, paralysis of the heat-inhibiting centers, paralysis of the thermogenic inhibiting centers in the spinal cord, dehydration, pharmacodynamic action of the minute doses of atropine which excite the vagosympathetic system stimulating the secretory function of the glands, chiefly the thyroid, the resultant transient hyperthyroidism accelerating metabolism, and producing abnormal heat, and last by a hypersensitivity to the drug.

Dryness, meaning dryness of the mouth and throat, diminution of saliva, thirst, difficulty in swallowing, and a dry skin are produced by suppression of the glands of secretion, i.e., salivary, sweat, lacrimal, mucous, gastric, and pancreatic. These actions are localized in the receptive substance on the nerve endings and are mutually antagonistic to pilocarpine. The flush, red skin, and eruption are due to the dilatation of the cutaneous vessels. The other symptoms probably come first from stimulation of the higher centers (excitement, delirium, visual hallucinations, and staggering gait), and second from depression of the central nervous system (coma, convulsions, and death).

## TREATMENT

Therapy is still unsatisfactory. Atropine in small doses is antagonistic to morphine, but, when used in larger quantities, its action on the higher centers becomes very similar to that of morphine in producing severe depression. Therefore, morphine should be used with great caution, or better not at all.

The parasympathetic drugs (pilocarpine, physostigmine, acetylcholine, and muscarine) are antagonistic to atropine and should be used in all cases of poisoning. The usual dose is 10 mg, of pilocarpine

repeated every half hour until the mouth is moist. The necessary amount is said to vary from fifteen to thirty times the amount of atropine that has produced the poisoning. It must be remembered that atropine paralyzes the nerve endings, and since the parasympathetic drugs act mainly through the nerves themselves, their benefit is doubtful, especially when large doses of atropine have been given. Cerebral stimuli should be given as in poisoning by morphine.

The extremely high temperature must be controlled by sponges, ice packs, cold enemas, and moist sheets. Fluids should be forced. The bladder should be catheterized for there is often urinary retention and there is the possibility of reabsorption of the atropine from the bladder walls. The stomach should be lavaged to remove any atropine that might be present. Strong tea or tannin solution or, if these are not available, a weak solution of iodine should be used to precipitate the remaining alkaloid in the stomach. Finely powdered charcoal may be used to adsorb the poison.

Sedation, if used, must be used cautiously for if the poisoning is severe enough, the added sedation plus the depressing action of the atropine on the higher centers will only aggravate the existing condition.

#### SUMMARY

- 1. Atropine, though used with impunity in varied conditions, may cause poisoning: it also occurs in wild plants in sufficient amounts to cause poisoning if they are eaten.
- 2. Poisoning has occurred in adults with doses of less than 1 mg., 12 and fatalities with 2 mg. In children fatalities have been reported from 0.4 mg.
- 3. Four drops of a 1 per cent solution of atropine contain 2 mg.  $(\frac{1}{20} \text{ gr.})$  of the drug.
- 4. Toxic symptoms: Hot, dry, flushed skin, dilated pupils, nausea, diarrhea, delirium, staggering gait, and coma.
- 5. Treatment consists of administration of parasympathetic drugs until the mouth is moist, copious lavage of the stomach, cerebral stimulants if coma is present, and catheterization of the bladder. High temperatures should be controlled by alcohol sponges, forced fluids.

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## DIAGNOSIS OF CONGENITAL SYPHILIS

## PATHOGNOMONIC CRITERIA

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IT IS of great importance that the diagnosis of syphilis, whether con-I genital or acquired, be certain before treatment is started because of the prolonged, expensive, and heroic specific therapy which is essential for its cure. In the case of acquired syphilis, an ordered procedure for absolute diagnosis has been developed and is in general use.1, 2 In congenital syphilis, for reasons to be elaborated upon later, no comprehensive diagnostic code has been established. Diagnostic criteria vary greatly in different communities.2-6 The purpose of this paper is to review and evaluate existing means of diagnosis and to attempt to formulate an outline of pathognomonic criteria.\*

Before the era of treatment for syphilitic pregnant women, congenital syphilis among the infants born of these women was both common and severe. Stillborn and heavily infected premature nabies were of frequent occurrence. In full-term infants snuffles and skin rashes soon developed; they are poorly, failed, and died. It was the exceptional infant who remained healthy and did not manifest symptoms of his mother's disease. In 1924 routine blood Wassermann tests and appropriate treatment. when indicated, became the rule among the pregnant women presenting themselves at the Stanford University Maternity Clinic. preceding 12 years, 26 per cent of the 224 fetal deaths were caused by syphilis. In the following decade syphilis accounted for only 2 per cent of 162 fetal deaths. This experience indicated the profound effect of prenatal treatment on the incidence of the fatal forms of neonatal con-McCord's extensive experience<sup>10</sup> with living infants genital syphilis. born of syphilitic women illustrates that severe infections are rare, mild infections uncommon, and complete freedom from infection, the rule, when proper prenatal treatment has been given. He states, "Regardless of the activity of the disease, sufficient ante-partum antisyphilitic treatment assures the woman a syphilis-free baby in 95 per cent of the cases." There can be no question of the profound effect of ante-partum treatment in preventing congenital syphilis.7, 11, 12, 13 Moore1 says: "Congenital syphilis is as nearly a preventable disease as smallpox."+

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\*Most American and English authorities!. 5, 5, 5 require proof of the presence of congenital syphilis before instituting treatment. The German authority Hoffmann' advocates treatment on suspicion "of all newborn children of mothers who are still intections or in whom infection is suspected." Hoffmann' also recommends "that the wives of infected men receive a sufficiently energetic preventive treatment in order to avert familial syphilis, for in this way the infection of the offspring is precluded."

the great an authority as Stokes' makes the disturbing, but fortunately unsupported, infantile into tardite heredosyphilis."

Granted the profound benefits to the unborn infant of maternal treatment during pregnancy, it is of fundamental importance to know the modus operandi of the ante-partum antisyphilitic medication if the status of the infant is to be properly appraised. Is infection of the fetus prevented or is an infected fetus "cured"? Continuous bimetal treatment instituted before and continued throughout pregnancy in all probability prevents infection of the fetus. It is generally believed that the product of conception in an untreated syphilitic woman is not infected before the fifth month of gestation. Such embryos as have been examined up to this period of pregnancy have without exception appeared to be nonsyphilitic.3 Thus it is apparent that treatment started before the fourth or fifth month of gestation prevents infection of the child. has been shown that treatment given only during the last trimester of pregnancy increases the chances that the infant will be viable at birth and will develop no evidence of syphilitic infection. A considerable, but indeterminate, number of such infants may represent instances of congenital syphilis "cured" in utero. If this concept that intrauterine treatment of the infected fetus results in a lasting biologic cure in some cases is correct, then one must face the reasonable possibility that other infants will be born partially treated and will present the difficulties of diagnosis which often surround the partially treated disease in acquired syphilis.\*

The diagnosis of congenital syphilis, once concerned principally with severe and relatively easily recognized cases, has been rendered much more difficult as a result of the nearly universal use of ante-partum treatment in infected women.3, 4, 6, 7 A more refined and judicious use of diagnostic methods is necessary now in order to identify the occasional mildly infected infant among the many syphilis-free babies born of Coincident with the diminished frequency treated syphilitic, mothers. and severity of congenital syphilis, there must come a change in attitude toward the newborn babies of syphilitic women. Whereas previously the baby was properly considered probably syphilitic, now the infant may be regarded as nonsyphilitic until proved otherwise. At one time it was perhaps excusable to give antisyphilitic treatment to all babies born of syphilitic women; only the exceptional infant was unjustly exposed to the dangers and disadvantages of unnecessary treatment. attitude now would be an injustice to most of the babies.

The diagnosis of bacterial disease is most satisfactorily established by identifying the causative organism. Lacking this criterion, one must rely upon specific and exclusive changes in the body tissues or fluids. In either proving or disproving the presence of syphilis, every ease must be

<sup>\*</sup>It does not necessarily follow, however, that the percentage of intrauterine "cures" will be the same as in cases of acquired syphilis receiving comparable amounts of treatment. This point will have to be illuminated by the results of prolonged follow-up study. There is reason to suspect that syphilis is more easily "cured" in utero than in any period of extrauterine existence. If this is shown to be true, then many infants whose cases are evaluated by the diagnostic criteria of Hoffmann<sup>3, 9</sup> are unjustly exposed to the hazards, expense, and discomfort of treatment.

judged on its own merits. "The diagnosis of syphilis must depend on the examination of the individual under consideration." A definitely positive or negative diagnosis cannot be established in the individual case by statistical probabilities.

There are three main methods of investigation by which the unquestionable presence or absence of congenital syphilis in living infants or children may be definitely determined:

- (1) bacteriologic examination
- (2) serologic examination
- (3) roentgenologic osseous examination

Clinical evidences of syphilis are purposely not included as of absolute diagnostic reliability. Jeans's states, "Few of the clinical manifestations of [congenital] syphilis are pathognomonic." Typical florid syphilis may be diagnosed by physical examination alone, but in such cases bacteriologic, serologic, or roentgenologic proof is also present. other hand, many syphilitic babies at birth show either no physical signs of the disease or only suspicion-arousing signs. The maternal history is valuable as a suspicion-arouser, but it cannot be relied upon for absolute diagnosis. The same remarks apply to the results of examination of the placenta. In florid syphilis the placental changes are often diagnostic, but in the physically negative syphilitic baby examination of the placenta will seldom give conclusive evidence for or against the presence of congenital syphilis.14 McKelvey and Turner7 found that in approximately 9 out of 10 cases in which there were syphilitic changes in the placenta, the child was syphilitic also, but only 19 per cent of these infants were viable at birth and in an even smaller fraction were evidences of syphilis in the child "masked."

Bacteriological Examination.—Unfortunately it is not often possible to find T. pallidum in living congenitally syphilitic children. When the spirochete is easily found, the infection is usually heavy, and the diagnosis is readily established by other means. Complete diagnostic reliance may be placed upon the presence of T. pallidum in dark-field preparations from skin lesions, but opportunities to examine material from open lesions in congenital syphilis are seldom encountered after the first few months of life. Material from mucous membrane lesions may contain T. microdentium or T. macrodentium, harmless spirochetes which must not be confused with T. pallidum.

Ingraham<sup>15</sup> has recently revived interest in dark-field examination of scrapings from the wall of the umbilical vein. In 6 of 8 stillborn syphilitic infants the examination revealed the presence of the spirochetes. Of 87 living infants born of syphilitic women but showing no evidence of syphilis on physical examination, the umbilical vein scrapings were positive in 19 cases. Seventeen of these 19 infants and 18 of the remaining 68, in whose cases spirochetes were not demonstrated in the scrapings, were all shown by other means (presumably serologic and

roentgenologic) to be actually infected. Thus a positive result from the scrapings of the wall of the umbilical vein in accordance with Ingraham's technique showed a 90 per cent correlation with the presence of syphilis, but the test was negative in about 50 per cent of the infected babies. A larger series than Ingraham's is necessary to establish definitely the reliability of a positive test in proving infection in the infant. Ninety per cent is probably too low a figure for the actual reliability of a positive result with this diagnostic method. Certainly, if facilities for this type of examination are available, they should be used at least in those cases in which infection of the infant is probable on the basis of maternal history and treatment.

Serologic Examinations.—There is overwhelming evidence that Wassermann reagin may be present in the circulating blood of newborn infants born of syphilitic mothers without the concomitant presence of spirochetes in the infant's tissues. 1, 2, 4, 7, 12, 13, 16, 17, 18 Presumably the reagin, by passive transference, crosses the placental barrier from the maternal to the fetal blood. Thus a nonsyphilitic newborn infant may have a positive blood Wassermann test. One effect of maternal ante-partum treatment, in our experience, has been an increase in the proportion of nonsyphilitic Wassermann-positive newborn infants.

A number of investigators have discontinued making Wassermann tests on newborn babies' blood because they deem the test "unreliable" in this age group. 16, 19 In 1936 we<sup>17</sup> showed that by titration the Wassermann test could be made roughly quantitative and that the quantity of reagin gradually fell to, and remained at, a subreactive level in non-syphilitic Wassermann-positive newborn infants. Usually reversal occurs within two or three weeks, 17, 18, 20, 21 but it may take at least as long as 70 days (Case 1). The greater the amount of reagin, the slower is complete reversal.

In the asymptomatic syphilitic infant reagin may be entirely absent at birth, but it will be present within a few weeks or at most within four months. More commonly the first serologic test will be positive. The reagin responsible for this early positive test may be either maternal or fetal in origin or may be a mixture of both maternal transplacental reagin and native fetal reagin. In general, titers tend to be higher in infected than in uninfected infants. If the cord blood reagin titer exceeds by a wide margin the maternal level, one cannot escape on theoretical ground the probability that the infant is syphilitic. There is as yet not enough clinical support to consider this observation of pathognomonic significance. Serologic differentiation between the infected and non-infected newborn infants depends, in our present state of knowledge, upon an increase in the amount of the reagin in the infected baby.

Our experience subsequent to our original report has confirmed our findings. Rising amounts of serum reagin in the asymptomatic physically negative syphilitic infant, followed by the development of snuffles, an

ulcer of the umbilicus, and the finding of spirochetes in material from the nose and umbilicus, have been observed. Prompt healing followed treatment (Case 2). An unequivocal rise of the blood Wassermann reagin titer is, in our opinion, positive proof of syphilis. The diagnostic value of the quantitative Wassermann tests has been substantiated by Christie.<sup>21\*</sup>

A newborn syphilitic baby may have a negative blood Wassermann test. In our personal experience such an occurrence is uncommon, but in other localities the seronegative syphilitic infants apparently constitute a frequently observed and diagnostically difficult problem.3, 6, 13 We have never encountered an infant who was seronegative at two months of age and seropositive later. This coincides with the experience of Cooke and Jeans.<sup>12</sup> In a series of 273 cases of syphilis in children, Roberts<sup>13</sup> encountered 103 infants with negative cord blood Wassermann reactions. Twenty-seven of these infants had subsequent negative blood tests, but only two of these negative tests occurred after the fourth Thus Roberts states, "These observations seem to justify the conclusion that it is probable that an infant born of a syphilitic mother, reaching the fourth month of life without physical or serologic evidence of the disease will escape the infection." The fear has been expressed that a child may occasionally be continuously seronegative and physically negative for years and eventually develop "tardive" congenital syphilist No conclusive cases of this type have been recorded. This fear is perhaps to a large extent carried over from the pre-Wassermann era when the seropositive, physically negative case could not be diagnosed till clinical "tardive" syphilis developed. We may then state that in our present state of knowledge two consecutive negative blood Wassermann tests and one negative spinal fluid Wassermann test in an untreated infant six months of age rule out congenital syphilis. McKelvey and Turner recommend periodic serologic tests for a year or two longer. At any time after the first four months of life, two consecutive properly done, strongly positive, blood Wassermann tests are absolute proof of syphilis. Most anticomplementary Wassermann tests occur in cases It is not improbable that congenital syphilis occasionally of syphilis. "eures itself." How often this occurs cannot be stated. Rarely, in older children or young adults who have never received any specific treatment. the blood is seronegative, and there are no physical signs of congenital syphilis except for typical Hutchinson's teeth. If the spinal fluid is like-

<sup>\*</sup>Accumulating evidence seems to indicate that in the neonatal period the significance of the blood Wassermann test differs from that of the Kahn, Kline, or Hinton test. In the cases reported in 1936" and in subsequent examples of seropositive nonsyphilitic newborn infants, we have found the Hinton test to be positive much less frequently than the Wassermann test. Gregor and Dellar" d about one-third as many positive Kahn and Kline reactions as reactions in their seropositive nonsyphilitic newborns, and Robi reactions whose cord blood Wassermann reactions are positive. We are not yet sure that slight hemolysis may not have played a part in our comparative results with the Wassermann and Hinton tests.

the great an authority as Stokes makes the disturbing, but fortunately unsupported, fantile into tardive heredosyphilis"

wise negative, treatment should not be given. Because of the great specificity of the Hutchinson's tooth, spontaneously "cured" congenital syphilis may be diagnosed in these cases. However, less than 1 per cent of the 521 syphilitic infants and children between the ages of 2 weeks and 15 years seen in the twenty-year period from 1914 to 1934 at the Harriet Lane Home of the Johns Hopkins Hospital in Baltimore had negative blood Wassermann reactions.<sup>23</sup>

Roentgenologic Osscous Examination.—Disregarding for the moment the question of possible or probable specificity, it must be acknowledged that roentgenologic findings are necessarily a much less direct form of diagnostic evidence in a bacterial disease such as syphilis than is the identification of the living organism or the positive specific spirochetal serologic reaction. Pathognomonic significance can be placed only upon those roentgen changes which by histopathologic, serologic, or bacteriologic correlation can be shown to mean active syphilitic infection. Furthermore, the roentgenologic diagnostic evidence must be of such definite and unequivocal nature as to permit no great differences in individual interpretation. In this connection the following remarks from Cooley and Reynolds24 are pertinent: "The use of the x-ray for diagnosis has by no means attained the status of an exact science. Its value in any particular study must depend on the interpreter's understanding of the physical characteristics and limitations of the method itself, and of the pathologic states in question and the physical effects to be expected from them. To attain the highest degree of accuracy in the reading of films requires a combination of knowledge of the roentgenologist, the clinician, and the pathologist, and either roentgenologist or clinician will be successful in proportion to his competence in all these fields. It is to be assumed that each of these several observers has made painstaking effort to qualify himself in these respects, and the fact that they so often fail to agree must be looked upon as evidence that we have not as yet learned to use the x-ray as an instrument of precision."

The diagnostic roentgenologic osseous changes in congenital syphilis have been most definitely defined in the English and American literature by McLean.<sup>25</sup> However, McLean himself did not look upon roentgenologic studies as of premier reliability. He states that it is not "suggested that roentgenology will ever assume the place now held by serology in the diagnosis of the disease," and further, "it is only by the correlation of clinical, serologic and roentgenologic observations that knowledge of congenital syphilis will be furthered." His thorough, critical, and widely accepted study concerned itself with 102 cases of congenital syphilis. That the average intensity of infection in his cases was great is shown by the mortality of 42.1 per cent. In 24 cases, the bones were examined histologically. In 96 cases in which serologic tests of the blood were made (mainly Kahn and Noguchi tests), the results were positive in 95, anticomplementary in 1, and negative in none. In only

17 cases (16.6 per cent) were clinical evidences of syphilis "masked." Hence McLean based his study on a group of cases of severe congenital syphilis. In only 2 of the 102 cases was a positive roentgenologic diagnosis made before the positive serologic findings were obtained. In one of these two, a positive blood test was obtained two days after the roentgenologic diagnosis was made. This certainly does not prove that bone changes actually preceded serologic changes. In the other case, an infant six weeks old, slight bone changes which were passed as "negative for osseous syphilis" by "an experienced roentgenologist" were present when the Kahn test was negative. At 10 weeks of age, the presumptive Kahn test was 4+, 4+, 4+. At 31/2 months, roentgenologic examination showed a marked progression of the osseous changes. The early bone changes in the light of subsequent serologic and roentgenologic events were undoubtedly related to syphilitic infection in this case, but a positive diagnosis of syphilis could scarcely be made on the basis of these early minimal and possibly nonspecific bone changes alone.

On the basis of his experience, McLean listed ten types of roentgenologic osseous changes which he considered diagnostic "on roentgen evidence alone" of congenital syphilis in the first months of life:

- "1. Well-defined saw-tooth metaphysis in well calcified bones
  - 2. Deep zones (in the longitudinal axis) of submetaphyseal rarefaction
  - 3. Multiple 'separation of epiphyses' with or without impaction in bones which are not rachitic
  - 4. Bilateral symmetrical osteomyclitis of the proximal mesial aspects of the tibiae
  - 5. Multiple circumseribed osteomyelitis of the long bones shown by the roentgen rays as patchy areas of rarefaction
  - 6. Multiple longitudinal areas of rarefaction (osteomyelitis) in the shafts of the long bones, sometimes resulting in fractures
  - 7. Destructive lesions at the mesial or lateral aspects of the metaphyses (foei of rarefaction)
  - 8. Multiple areas of cortical destruction generally seen within a centimeter of the ends of the bones.
  - 9. Double zone of rarefaction at ends of bones
  - 10. Localized periosteal cloaking occurring in more than one bone."

These diagnostic criteria have been widely accepted since their formulation in 1931. Obviously bone changes as seen on the roentgenogram must have modest beginnings, and McLean recognized the nonspecificity of the earliest changes, i.e., increased density of the zone of temporary calcification, and mild or moderate degrees of proximal rarefaction.

Criteria 1, 3, 4, 5, 6, 7 and 8 are still accepted as pathognomonic. A very high degree of technical perfection in making the roentgenogram is necessary for clear and unequivocal demonstration of criterion 1. Simple increase in the density of the metaphysis is definitely not diag-

nostic of syphilis according to McLean. In criterion 7 the changes should be multiple and very definite.

There is perhaps some question as to whether criteria 2, 9 and 10 are sufficiently reliable to retain their pathognomonic significance. As for criterion 2 we feel, even on McLean's personally reported experience, that perhaps it should not be included in its present form as a sign by which a definite diagnosis of congenital syphilis can be made "on roentgen evidence alone." Minor and sometimes rather marked degrees of submetaphyseal rarefaction occur in anemia in infants and in other conditions in early life in which growth has been disturbed. should be perceptible disturbance of bone architecture before diagnosing syphilis on this criterion. I would suggest that this criterion be changed to read: "Deep zones (in the longitudinal axis) of submetaphyseal rarefaction with perceptible disturbance of cancellous bone architecture." As in criterion 1, a high degree of technical perfection in making the roentgenogram is necessary to demonstrate this point unequivocally. The conditions of criterion 9 may be simulated occasionally by nonsyphilitic states and by two, spaced, antenatal or postnatal courses of bismuth.26 An example of the changes of criterion 10 occurring in a nonsyphilitic infant in the second month of life is reported in a subsequent paragraph (Case 3). So for criteria 2, with suggested change in phrasing, 9 and 10, we desire diagnostic confirmation from serology, bacteriology or roentgenology (by definite progression of the osseous changes) before an absolute diagnosis may be made.

Several investigators have recently reported that changes in the skeleton occur with surprising frequency in seronegative and physically negative infants born of syphilitic women, and have concluded that the osseous changes as shown by the roentgenogram are not infrequently more delicate indicators of the presence of syphilitic infection than are serological findings. If these observations and conclusions, never anticipated by McLean himself, are conclusively shown to be true, they will revolutionize present-day concepts of the pathogenesis of congenital syphilis, and dim the apparent brilliance of the results of ante-partum prophylaxis.

In view of the fact that the case material of these recent astonishing reports is not comparable to McLean's case material, it follows that the conclusions of the latter do not necessarily apply directly to the former. Parmelee and Halpern's reported material which in their opinion showed a marked superiority of osseous changes over serologic findings in the diagnosis of congenital syphilis throughout the first year of life. They report that the roentgen examinations were "positive" in 95 per cent of the infected infants, whereas the serologic tests were positive in only 29 per cent. The paper contains no individual case reports, no reproductions of roentgenograms, no statement of minimum diagnostic roentgenologic signs. no correlation with maternal treatment, no reports of

spinal fluid examinations, and no necropsy proof. The report is based on the cases of 104 infants, 79 of which were properly studied at birth, 60 at six weeks, 35 at three months, 23 at six months, and only 8 at 1 year. Sixty-seven cases (64 per cent) were considered "positively infected." In the discussion at the end of the paper some light is thrown upon the probable source of error by the following statements: "The earliest manifestation is the thickened epiphyseal line with a narrow zone of rarefaction immediately shaftward in the metaphysis" and "if physicians become familiar with the roentgenologic signs of syphilis, they will find a surprisingly large number that do show some evidence of syphilis." Hence the minimum roentgenological change considered "positively" diagnostic was apparently "the thickened epiphyseal line with a narrow zone of rarefaction immediately shaftward in the metaphysis."

McLean warns specifically against accepting increased density of the zone of temporary calcification and mild or moderate degrees of submetaphyseal decalcification as diagnostic of congenital syphilis. He says, in referring to the former, "It has been my experience that the roentgenologist should be cautious about making a diagnosis of syphilis on this evidence alone." Of the latter, he states "... it does occasionally occur in conditions other than syphilis. . ," and further, "although the roentgenologist is willing to defer to serology and clinical manifestations for the diagnosis of syphilis in a case showing the aforementioned osseous changes . . . he cannot make an unequivocal diagnosis of the disease on this roentgen evidence alone." Even in syphilitic infants, these two changes, McLean states, "may not be due to any local action of the spirochetes, but to the systemic effects of the disease on the blood" and may thus be nonspecific. Caffey26 has recently shown that maternal ante-partum injections of bismuth may produce dense fetal metaphyseal lines, another source of error for the unwary.

Another report worthy of comment is Ingraham's paper, "Roentgen-Positive Seronegative Infantile Congenital Syphilis." He states that during the course of the study of 134 selected cases there were "only nine in which the diagnosis of congenital syphilis was suggested by routine physical examination and serologic study before the x-ray films revealed lesions in the bones. In this same group roentgenographic evidence of bone changes which have been described as characteristic of congenital syphilis was found in 49 cases (36.5 per cent) . . . in 26 cases (19.4 per cent) at six days, before discharge from the maternity division, and in 23 additional cases (17.1 per cent) at ages from 1 to 10 months." No statement is made to indicate what were considered to be minimum diagnostic roentgenologic signs, and there is no table or other record to show the results of simultaneous scrologic and roentgenologic examinations in the group as a whole. Without these two bits of essential information, the paper loses much of its force; for the minimum roentgen

criteria may have been of such a minor nature as not to be acceptable as of established pathognomonic significance, and, if the serologic examinations were not made at about the same time as the roentgenologic examinations, it would be impossible to determine which developed first, diagnostic roentgen changes or positive serologic reactions.

There are eight illustrative case reports in this paper. Case 1 is that of a normal newborn infant used as a control. Case 2 is that of a syphilitic baby, seronegative at birth, roentgen positive at three weeks of age, and roentgen-positive at three months. Apparently no Wassermann or other serologic test was made except at birth. It is quite possible that the serologic reaction was positive at the time the first roentgen examinations were made. Case 3 is that of an infant born of a woman who acquired syphilis when three months pregnant. She had received eight injections of neoarsphenamine in the latter part of pregnancy. The infant was seronegative at birth and had no further blood test till she was three and one half months of age. At this time the serologic reaction was strongly positive and florid syphilis was apparent. At six days of age an osseous roentgenogram revealed slight suspicion arousing nondiagnostic changes which at three and one half months had progressed to extensive lesions. This case, like Case 2, merely shows that a baby who is seronegative at birth may be syphilitie. Since the mother's infection occurred during pregnancy, this infant should have had more frequent blood Wassermann tests. Case 4 is that of an infant whose mother was infected late in pregnancy and received no ante partum treatment. The cord blood Wassermann reaction was positive. At six weeks of age the infant was seronegative. No further serologic tests were done till the infant was four and three quarters months old at which time the reaction of the blood was found to be strongly positive. Roentgenograms at buth showed minor bone changes. At two and one half months and at five months these changes had progressed to pathognomome syphilitic lesions. Again in this case, the lack of simultaneous blood and roentgenologic examinations vitiates the conclusion that diagnostic bone changes preceded positive serologic changes. It is certain that this infant was infected either shortly before or at birth. Possibly circulating Wassermann reagin had passed the placenta from the mother's circulation before parturition and then disappeared before the infant's own reagin began to rise about six weeks later. We are not willing to accept the "narrow band of sclerosis at the distal metaphysis" and "nairow band of rarefaction proximally." which were noted at six days of age, as pathognomonic of syphilis even though the clinical probability that the infant was infected is overwhelming in a special case of this soit. In Case 5, it is not clear from the protocol whether the negative blood reactions were obtained at three months or at five months of age. Judging from the description, the bone changes were rather bizarre. There is no doubt that the infant was syphilitic. A negative blood test in a severely infected infant of this age is so remarkable that it would have been wise to have repeated the blood test to rule out any possible error. This case presents the most convincing evidence of the entire group, of the failure of serology to indicate infection, but even here the positive results of the dark field examination and not the peculiar coentgenologic changes are the conclusive proof of infection. This infant may have had acquired, not congenital, syphilis, for the mother showed no evidences of infection. If this were the case, the positive dark field findings were perhaps obtained during the early seronegative phase of acquired syphilis. In Case 6 the cord blood Wassermann reaction was negative. At three months the infant had florid syphilis; the Wassermann reaction was positive, and there were definite marked roentgenologic changes typical of osseous syphilis. This case merely shows that an infant with a negative cord Wassermann reaction may have syphilis. Since the mother was known to be syphilitic and had received no treatment during this pregnancy, the baby's blood should have been checked more frequently. In Case 7 the infant was not proved to be syphilitic although the mother was infected. The infant was seronegative at two months, at which time a ray examination showed "marked flaring and sclerosis of the distal metaphyses of the radius and ulna bilaterally. There was periorities on the outer aspects of both femure and both tibias." This description does not correspond well with any of McLean's diagnostic criteria. Case 8 describes a congenitally deformed infant who died of pneumonia. Both mother and infant were physically and serologically negative. However, the description of the roentgenologic osseous changes in the infant seems to be characteristic of congenital syphilis. Without a postmortem examination report, the specificity of the bone changes may perhaps be questioned

In another report appearing at about the same time as the one just discussed, Ingrahamo presents the material in somewhat more detail Especially worthy of comment is the table showing the effect of maternal treatment on the incidence of syphilis in the child Syphilis was diagnosed in 482 per cent of the infants boin of women who were treated for from four to eight weeks during pregnancy, whereas McKelvey and Tunner diagnosed syphilis in only 202 per cent of the offspring of women receiving the equivalent of three to six weeks of treatment (1 to 2 gm of arsphenamine in 03 gm doses weekly) during pregnancy A relatively small part of this marked difference might be due to the difference in drugs employed, but this should be more than offset by the one to two weeks (approximately 30 per cent) longer periods of treatment of Ingraham's cases In eases in which there was no prenatal treatment, Ingraham diagnosed syphilis in 798 per cent of the infants whereas McKelvey and Turner found 646 per cent to be syphilitic In cases in which there were more than thirteen weeks of ante-partum treatment, McKelvey and Turner found no syphilis, whereas Ingraham diagnosed syphilis in three of twenty similar cases (15 per cent) So under all conditions of ante-partum treatment, but especially in the middle ranges. Ingraham diagnosed syphilis in the offspring much more frequently than did McKelvey and Turner The difference is due primarily. I believe, to Ingraham's over-refined roentgen diagnostic criteria \*

Thus the reports of Parmelee and Halpern and of Ingraham do not, in our opinion, prove the superiority of roentgenology over serology in the diagnosis of congenital syphilis. In all three reports, 6, 2 an attempt has been made to attach pathognomonic significance to the earliest discernible roentgenologic changes in the bones. That these minor changes are often related to syphilitic infection is not to be argued, but at this stage the changes may be due to causes other than syphilis. They should certainly be looked upon as suspicion-arousing but not, in our present state of knowledge, as diagnostic signs. Whether or not the individual infant showing these changes is syphilitic will be proved by subsequent serologic, roentgenologic, or bacteriologic examination and occasionally

<sup>&</sup>quot;The majority of Ingraham's and of McKelvey and Turner's patients were negroes from Philadelphia and Bultimore, respectively

by physical signs Repeated bone studies are less readily available than repeated serologic tests, and the results more equivocal; hence the serologic tests are in general more practical

Our personal feeling concerning the probable significance of a little increased density in the zone of temporary calcification and/or slight or moderate degrees of submetaphyseal rarefaction in the long bones of young seronegative and physically normal infants born of suphilitic women is as follows:

- (a) The changes will occur occasionally in infants born of nonsyphilitic women.
- (b) In cases of infants whose mothers have received moderate or large amounts of ante partum treatment, diagnostic evidences of active syphilis will seldom develop, and the changes in the bones will disappear within a few weeks. Perhaps these are cases of congenital syphilis "cured" in utero
- (c) In cases in which there has been no ante partum antisyphilitic treatment a considerable number of the infants will within a few weeks be diagnosable syphilitic. The positive diagnosis will be more simply and conclusively demonstrated by blood tests repeated at ten day intervals than in any other way.

There is still a need for two types of study—first, simultaneous serial identification and serologic examinations of newborn infants in whom syphilis is suspected and, second, investigation of the frequency and nature of identification bone changes in normal infants, and in various nonsyphilitic pathologic states during the first three or four months of life

## DISCUSSION

It is certainly not malpraetice to insist upon a positive diagnosis before undertaking the treatment of syphilis Indeed one of the important axioms of the proper management of this disease is that the diagnosis must be established before treatment is instituted I have no argument with those who advocate treatment on strong or even on weak suspicion of the presence of the disease, but I do contend, in the interests of science and the advancement of our knowledge of the nature of the infection, that a sharp distinction should be drawn between a positive and a presumptive diagnosis of congenital syphilis. The use of the schema of diagnosis outlined in this paper (Tables I, II and III) will establish the presence or absence of syphilis in nearly all babies within three weeks after birth. Occasionally it will not be possible to make a positive diagnosis in an infected infant for a period of six weeks or two months after buth Does this delay in instituting treatment in an apparently healthy but actually infected infant jeopardize the chances of ultimate cure? Although theoretically undesirable, there is no evidence that this amount of delay in such cases is haimful. There are perhaps occasional instances in infancy in which one would be justified in beginning treatment without the support of an absolutely positive diagnosis Should such a situation arise, consultation with the best available authority in each of the fields concerned (roentgenology, pediatries, and serology) should be obtained.

## SUMMARY

Criteria accepted as diagnostic of congenital syphilis vary widely in different communities. There are many suspicion-arousing, but relatively few pathognomonic, circumstances, signs or symptoms of congenital syphilis. Pathognomonic evidence of the presence of syphilis in living infants and children is seldom afforded by the results of physical examination but is to be found in the results of properly interpreted dark-field, serologic and roentgenologic examinations. A critical analysis of the significance of the results of these diagnostic methods has led to the formulation of a tentative pathognomonic code as presented in Tables II and III. Table I offers a suggested chronological order of procedure for the recognition of syphilis in young infants. Three case reports are included to illustrate and emphasize the application and interpretation of certain diagnostic methods.

## TABLE I

PROCEDURE FOR THE DIAGNOSIS OF CONGENITAL SYPHILIS IN YOUNG INFANTS

I. Routine Wassermann test, history (with syphilis in mind), and careful physical examination (with syphilis in mind) of all pregnant women at the time pregnancy is diagnosed. Frequent check-ups of suspicious cases.

2. Suitable treatment of every pregnant woman who has or has had syphilis, regardless of the results of serologic tests, physical signs of the disease, or previous

treatment.

3. Dark-field examination of umbilical vein scrapings in every case in which there has been inadequate, irregular, or no ante-partum treatment.

4. Cord or peripheral infant blood Wassermann or other serologic test in every case and titrations in all positive cases. Without this original test, titrated when

positive, it is impossible to evaluate properly the next test.

5. Roentgenograms of the long bones within two weeks after birth of those infants in which the presence of syphilis is fairly probable (inadequate, irregular or no ante-partum treatment) or in which the first serologic reaction was positive.

6. Repeated infant blood Wassermann tests at not longer than two-week intervals

with titrations in cases in which the original test was positive.

7. Repeated roentgenograms at one month or six weeks of age in cases in which the diagnosis is still in doubt.

8. Repeated dark-field examinations of any suspicious lesions (mucous membranes of nose, mouth, or anus; diaper rash; slowly healing umbilical stump, etc.).
9. Spinal fluid examinations of infants in whom the presence of syphilis is fairly probable (see 5 above) when subsequent examinations have not revealed positive

diagnostic results.

## CASE REPORTS

CASE 1.-J. B., a girl, was born Dec. 4, 1934, at full term; the weight at birth was 2,820 gm. The mother stated that her mother and father had had syphilis; she herself was said to have been syphilitic at birth, but she did not receive treatment until she was 12 years old. In September, 1934, in the prenatal clinic, her Wassermann reaction was three-plus. She received thorough treatment for the remaining three months of her pregnancy, and she had no clinical evidence of syphilis and no history of distinctive lesions. The baby, though small, showed no evidence of disease, except that at the age of 15 days there was a small "macerated" area of excoriation on the perineum; this healed without specific treatment. Roentgenograms were made on Jan. 14, 1935 (age 6 weeks), and the bones of the arms and legs showed no evidence of syphilis. The results of Wassermann tests during the first three months of life are shown in Fig. 1.

by physical signs. Repeated bone studies are less readily available than repeated serologic tests, and the results more equivocal; hence the serologic tests are in general more practical.

Our personal feeling concerning the probable significance of a little increased density in the zone of temporary calcification and/or slight or moderate degrees of submetaphyseal rarefaction in the long bones of young seronegative and physically normal infants born of syphilitic women is as follows:

- (a) The changes will occur occasionally in infants born of nonsyphilitic women.
- (b) In cases of infants whose mothers have received moderate or large amounts of ante-partum treatment, diagnostic evidences of active syphilis will seldom develop, and the changes in the bones will disappear within a few weeks. Perhaps these are cases of congenital syphilis "cured" in utero.
- (c) In cases in which there has been no ante-partum antisyphilitic treatment a considerable number of the infants will within a few weeks be diagnosable syphilitics. The positive diagnosis will be more simply and conclusively demonstrated by blood tests repeated at ten-day intervals than in any other way.

There is still a need for two types of study: first, simultaneous serial roentgenologic and serologic examinations of newborn infants in whom syphilis is suspected and, second, investigation of the frequency and nature of roentgenologic bone changes in normal infants, and in various nonsyphilitic pathologic states during the first three or four months of life.

## DISCUSSION

It is certainly not malpractice to insist upon a positive diagnosis before undertaking the treatment of syphilis. Indeed one of the important axioms of the proper management of this disease is that the diagnosis must be established before treatment is instituted. I have no argument with those who advocate treatment on strong or even on weak suspicion of the presence of the disease. but I do contend, in the interests of science and the advancement of our knowledge of the nature of the infection, that a sharp distinction should be drawn between a positive and a presumptive diagnosis of congenital syphilis. The use of the schema of diagnosis outlined in this paper (Tables I, II and III) will establish the presence or absence of syphilis in nearly all babies within three weeks after birth. Occasionally it will not be possible to make a positive diagnosis in an infected infant for a period of six weeks or two months after birth. Does this delay in instituting treatment in an apparently healthy but actually infected infant jeopardize the chances of ultimate cure? Although theoretically undesirable, there is no evidence that this amount of delay in such cases is harmful. There are perhaps occasional instances in infancy in which one would be justified in beginning treatment without the support of an absolutely positive Should such a situation arise, consultation with the best available authority in each of the fields concerned (roentgenology, pediatrics, and serology) should be obtained.

## SUMMARY

Criteria accepted as diagnostic of congenital syphilis vary widely in different communities. There are many suspicion-arousing, but relatively few pathognomonic, circumstances, signs or symptoms of congenital syphilis. Pathognomonic evidence of the presence of syphilis in living infants and children is seldom afforded by the results of physical examination but is to be found in the results of properly interpreted dark-field, serologic and roentgenologic examinations. A critical analysis of the significance of the results of these diagnostic methods has led to the formulation of a tentative pathognomonic code as presented in Tables II and III. Table I offers a suggested chronological order of procedure for the recognition of syphilis in young infants. Three case reports are included to illustrate and emphasize the application and interpretation of certain diagnostic methods.

## TABLE I

# PROCEDURE FOR THE DIAGNOSIS OF CONGENITAL SYPHILIS IN YOUNG INFANTS

1. Routine Wassermann test, history (with syphilis in mind), and careful physical examination (with syphilis in mind) of all pregnant women at the time pregnancy is diagnosed. Frequent check-ups of suspicious cases.

2. Suitable treatment of every pregnant woman who has or has had syphilis, regardless of the results of serologic tests, physical signs of the disease, or previous

3. Dark-field examination of umbilical vein scrapings in every case in which there

has been inadequate, irregular, or no ante-partum treatment.
4. Cord or peripheral infant blood Wassermann or other serologic test in every case and titrations in all positive cases. Without this original test, titrated when

positive, it is impossible to evaluate properly the next test.

5. Roentgenograms of the long bones within two weeks after birth of those infants in which the presence of syphilis is fairly probable (inadequate, irregular or no ante-partum treatment) or in which the first serologic reaction was positive.

6. Repeated infant blood Wassermann tests at not longer than two-week intervals

with titrations in cases in which the original test was positive.

7. Repeated roentgenograms at one month or six weeks of age in cases in which the diagnosis is still in doubt. 8. Repeated dark-field examinations of any suspicious lesions (mucous membranes of

nose, mouth, or anus; diaper rash; slowly healing umbilical stump, etc.).

9. Spinal fluid examinations of infants in whom the presence of syphilis is fairly probable (see 5 above) when subsequent examinations have not revealed positive diagnostic results.

#### CASE REPORTS

CASE 1 .- J. B., a girl, was born Dec. 4, 1934, at full term; the weight at birth was 2,820 gm. The mother stated that her mother and father had had syphilis; she herself was said to have been syphilitic at birth, but she did not receive treatment until she was 12 years old. In September, 1934, in the prenatal clinic, her Wassermann reaction was three-plus. She received thorough treatment for the remaining three months of her pregnancy, and she had no clinical evidence of syphilis and no history of distinctive lesions. The baby, though small, showed no evidence of disease, except that at the age of 15 days there was a small "macerated" area of excoriation on the perineum; this healed without specific treatment. Roentgenograms were made on Jan. 14, 1935 (age 6 weeks), and the bones of the arms and legs showed no evidence of syphilis. The results of Wassermann tests during the first three months of life are shown in Fig. 1.

## TARLE IT

# TENTATIVE CRITICIA FOR POSITIVE DIAGNOSIS OF CONGENITAL SYPHILIS

- I. Diagnosis established by dark field examination (identification of two or more living T. pallidum in dark field preparations) A. At birth
- 1. In scrapings of the wall of the umbilical vein near the fetal end of the umbilical cord
  - B. After birth
  - 1 In material from skin or mucous membrane lesions
- II. Diagnosis established by serologic tests (properly done on suitable material) A. At birth

  - 1 High Wassermann leagin titel 2. Wassermann reagin titer unequivocably gleater than that of the maternal serum
  - B During first four months of life
    - 1 Negative test becoming positive
    - 2. Rise in titer on subsequent measurement of a positive serum
  - C. After four months
- 1. Strongly positive test (checked)
- 111. Diagnosis established by roentgenologic osseous examination (interpretation by a competent and experienced individual, preferably a radiologist)
  - A. At birth
    - 1. Changes of the sort described by McLean's criteria 1, 3, 4, 5, 6, 7, and S
  - B. At six weeks or later
    - 1. Same as III, A. 1
    - 2. Definite progression of osseous lesions as compared with those seen at about the time of buth and reaching the stage of McLean's criteria 1, 3, 4, 5, 6, 7, 8, and 10

#### TABLE III

## TENTATIVE CLITCHIA FOR ESTABLISHING THE ABSENCE OF CONGENITAL SAPHILIS IN UNTREATED INFANTS AND CHIEDPEN

- At birth
  - A Non-sphilitic mother
- 11. At four months
  - A. Two negative blood and one negative spinal fluid serologic reactions, properly done on suitable ma terial
- III After two years
  - A Two negative blood and one negative spinal fluid serologic reactions, properly done on suitable material

On May 15, 1935, the spin il fluid contained I I leucocytes per cubic millimeter, the reactions to the Nonne and Nogueli tests were negative; the Wassermann reaction was negative, and the colloidal gold curve was 1111100000

This infant has been examined physically for evidences of syphilis, and blood Wassermann tests have been performed at intervals, with uniformly negative results The last serologic and physical examinations were done on March 8, 1937, when she was 2 years and 3 months old

CASE 2 - This white male infant had three older siblings in all of whom the blood Wassermann reactions were negative. The father and mother were infected with siphilis when the mother was seven months pregnant, but their cases were undiagnosed and untreated until after the birth of this baby The patient was born at term with no physical evidences of syphilis, but the cord blood Wassermann test was positive Titration of the serum at 10 days showed a titer of between 10 and 19 units of At 12 days the umbilious was noted to be raw "with a markedly indurated hase " This may have been a chance Dark field examination was not done At 20

days the reagin titer was exactly 10 units, and the infant was still physically negative except for the umbilical lesion. At 50 days of age, nasal discharge had developed, and the umbilicus was still incompletely healed. The reagin titer had risen to between 20 and 40 units. Six days later the titer was exactly 40 units. At 69 days it was exactly 80 units. At this time spirochetes were found in the first examination of material from the umbilicus and nose, and a generalized lymphadenopathy was noted. The weight gain had been satisfactory. Treatment was instituted, and the lesions healed promptly. At the age of 120 days the reagin titer had fallen to 10 units (Fig. 2).

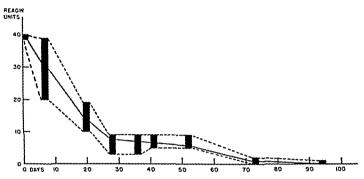


Fig. 1.—Case 1 Wassermann reagin titrations in a seropositive, nonsymbilitic infant. The black columns indicate possible range of reigin as determined by serum dilutions tested. The solid line approximates the probable true course of the serum reagin concentration, the broken lines indicate the theoretically possible maxima and minima.\*

<sup>\*</sup>See reference 16 for technique of estimating the seium reagin concentration and its expression in "units". Many closely gladed serum dilutions are necessary in strongly positive serums to obtain an accurate estimate of the amount of reagin present. Theoretically, the smaller the difference between successive dilutions the more exact will be the results.

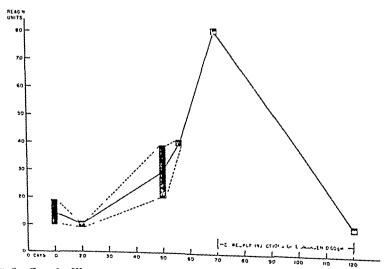


Fig. 2—Case 2 Wassermann reigin titrations in a case of proved congenital syphilis. (See interpretation of Fig. 1.)

The first roentgenograms of the bones were taken at the age of 5 weeks. The long bones of the legs appeared normal, but slight changes were seen in the bones of the arms. There was a narrow dense white line across the distal ends of the radius and

ulna Slight rarefaction of not more than 2 millimeters depth could be seen just proximal to the dense line at the lower end of the radius. The medial aspect of the shaft of the ulna showed a strip of periosteal density 1½ inches long and about 1 millimeter thick. Osseous roentgenograms were repeated at 4¾ months of age after 16 injections of 0.05 gm of bismarsen had been given. There was considerable density at the ends of all the long bones, measuring as much as 6 millimeters at the distal ends of the femure where it was most striking. This was interpreted as indicative of healing although it is possible that bismuth medication was responsible for some of the density.

Discussion—The umbilical lesion, which may have been a chance, probably would have yielded spirochetes when the infant was 12 days old, had the examination been made at that time. The rise of reagin to more than 20 units at 50 days of age was positive proof of syphilis. The bone changes which were apparent at 5 weeks of age were certainly syphilitic in character but they were not pathognomonic.

CASE 3—D S was a colored female infant, born on Aug 18, 1935, at full term The mother had had, by a previous husband, four children aged 13, 8, 7, and 5 year. The first and third were physically and serologically negative for syphilis The second and fourth had strongly positive blood Wassermann reactions, they had received no treatment and on physical examination showed no evidence of syphilis The mother had negative Wassermann and Kahn blood reactions during this pregnancy. Several weeks after delivery her blood calcium was 12 1 mg per cent, and roentgenograms of the pelvis showed normal bone structure. Nothing is known about this infant's father.

The baby was born at home. She was placed on an evaporated milk, water, and karo mixture. She gained weight, her skin was clear, and there was no nasil obstruction. She received a daily sun both

At 7 PM on September 25 when she was 5½ weeks old, one arm and leg twitched for 20 or 30 minutes. During the night the twitching recurred and involved other muscles. The free intervals became shorter and the attacks longer till September 29, when the spismodic muscle contractions became continuous, and the baby was brought to the Children - Hospital of Philadelphia. On admission the rectal tem perature was 99° F, the weight 8 pounds and 2 ounces. She was in a state of continuous clonic generalized convulsions. The fontanelle was normal, the skin clear, and the nose clean. She received two doses of 1 gm of calcium gluconate intra muscularly, 3 gm of calcium lactate daily by mouth, 15 drops of viosterol daily, and small repeated doses of phenobarbital. The convulsions gradually subsided in two days' time, but a positive Chyostek's sign and increased muscle tone persisted for two weeks.

The results of urinalysis, blood count, and spinal fluid examination were normal. The Wassermann and Kahn reactions of the blood and spinal fluid were negative The blood calcium (after the two injections of calcium gluconate) was 82 mg per 100 cc and the blood phosphorus was 58 mg per 100 cc. The blood sugar was 67 mg per 100 cc. On the second day after admission roentgenograms of the irms and legs showed a generalized periosteal clotking of the long bones and marked osteochondritis at the proximal and distal ends of the left tibia and at the distal end of the right humerus There were also scattered areas of less marked osteo chondritis and submetaphy-eal rarefaction. These changes were interpreted as characteristic of congenital syphilis by an experienced roentgenologist syphilitic medication was given. Eight days later (October 9) there was roentgen evidence of marked healing (Figs 2 and 4), which was considered complete 31/2 months liter (Jan 28 19 8), (Figs 5 and 6). The blood calcium and phosphorus were 12 6 and 65 mg per 100 c.c., respectively, on November 2, one month after ad mission. The blood Wassermann and Kalin tests were repeated every two weeks for

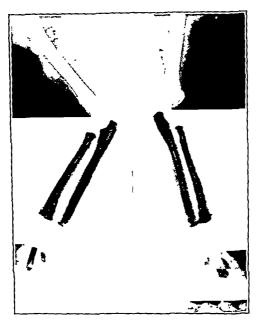


Fig. 3.—Case 3. Roentgenogram of arms at 7 weeks of age.

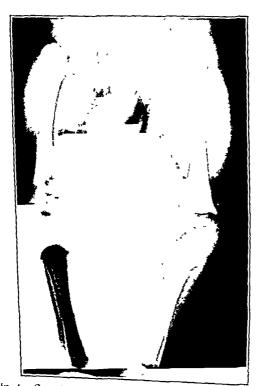


Fig. 4.—Case 3. Roentgenogram of legs at 7 weeks of age.

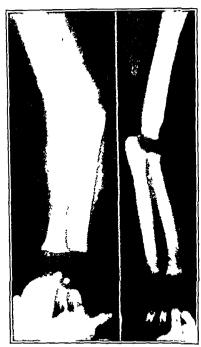


Fig. 5.—Case 3. Roentgenogram of arms at 512 months of age. The cortex of the long bones is thickened, especially in the midpart of the diaphyses.



Fig. 6 -Case 3 Roomgenogram of legs at 512 months of age.

two months and again at the ages of 5 and 31 months with uniformly negative The results of these tests were checked in other laboratories with the same results. negative findings.

Discussion .- This unique case demonstrates how contradictory, in the diagnosis of congenital syphilis, the serologic and roentgenologic findings may be. The convulsions were hypocalcemic in origin and were relieved by appropriate treatment. The extensive bone lesions healed, and the infant was physically, serologically, and roentgenologically normal at 5 months of age, without benefit of specific medication. At 21/2 years of age the blood Wassermann test was negative, and physical examination revealed no evidence of syphilis.

Moore speaks of the occurrence of "x-ray evidence of osteochondritis at birth in the absence of all other signs of syphilis" in infants born of syphilitic mothers treated during pregnancy. The bone lesions in these babies healed promptly, and no clinical or serologic evidences of syphilis appeared "during prolonged observation." Our case differs from these in that the mother received no prenatal treatment. Cregor and Dalton18 mention three infants, born of treated syphilitic women. which showed roentgenologic changes in the bones suggestive of syphilis. The infants were not treated and remained physically and serologically normal during fifteen, twelve, and eight months of observation, respectively.

I wish to express appreciation to Dr. H. K. Faber for his encouragement and advice in the preparation of this paper and to Dr. R. R. Newell for his critical assistance in preparing the section on roentgenologic examination.

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## BRONCHOGRAPHY IN CHILDREN

A SIMPLE METHOD ACCOMPLISHED WITH GENERAL ANESTHESIA

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In THE diagnosis of intrapulmonary conditions a bronchogram is frequently essential. An adult can usually be persuaded to submit to the instillation of oil under local anesthesia and will give the cooperation necessary to conveniently complete the procedure. With children, however, such cooperation is not readily obtained. Older children, especially those who have repeatedly been bronchoscoped, may submit to the instillation of lipiodol as readily as adults. Younger patients or those who are new in the hospital present difficulties which frequently are not overcome by any technique in current use.

The injection of oil through a large bore needle directly into the trachea by puncture through the skin of the neck is successful in many instances, but it has several serious objections. One is the frequent injection of oil into the peritracheal tissues which remains there indefinitely. Another is the occasional cellulitis developing at the site of puncture although this usually subsides without trouble. In one instance, however, the injection of oil into the peritracheal tissues was followed three weeks later by a retropharyngeal abscess and the child subsequently died from some form of respiratory obstruction. Autopsy not being obtainable, it was never determined what bearing the attempted bronchography had on the fatal outcome, but the feeling that it may have been an important factor caused us to abandon this procedure.

A review of the literature did not reveal a description of a method by which bronchography was accomplished with other than local anesthesia. It seemed advisable to investigate the possibilities of intravenous, rectal, and inhalation narcosis. The first important consideration was the selection of an anesthetic drug. It was imperative that the agent be nonirritating to pulmonary tissues, nonexplosive, sufficiently potent to obtund cough reflexes, simple to administer, and readily controllable. The possibilities of intravenous, rectal, and inhalation narcosis were investigated. The barbituric acid derivatives recommended for intravenous use were employed. It was determined that the anesthetic dose required to obtund the cough reflex of children closely approximated that dose which would cause respiratory arrest. Laryngospasm and bronchiolar spasm resulting from the parasympathetic action of these drugs make their use as anesthetics undesirable for bronchography.1 Rectal anesthesia was employed without entire satisfaction. Dangerously large doses of rectal barbiturates or of avertin in amylene hydrate may not obtund

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laryngeal or cough reflexes. In our experience it was always necessary to complement their action. Rectal ether is advised because it minimizes the dangers from explosions but is undesirable since it does not reduce materially the effects of the drug upon inflamed respiratory passages. It was not seriously considered.

An effort was then made to adopt a technique whereby bronchograms could be completed during general narcosis. It was soon obvious that modifications of the standard accepted techniques were needed to meet all the requirements. Finally a method of anesthesia was devised which combined basal narcosis with avertin in amylene hydrate by rectum, the local application of metycaine in the pharynx, larynx, trachea, and bronchi, and the administration of nitrous oxide and oxygen, employing an intratracheal airway. At first glance this seems like an unduly complicated procedure, but actually, in the hands of a trained anesthetist, it is simple. When anesthesia is established, it requires but a moment to instill the lipiodol. Compared with the tedious and irritating wheedling necessary to anesthetize the larynx and instill lipiodol in a refractory and apprehensive child, it is a quick and pleasant method.

The procedure is accomplished by first giving the patient a cleansing enema not later than six hours prior to the scheduled time of study. One and one-half hours before anesthesia, premedication with an appropriate hypodermic dose of codeine and atropine or morphine and scopolamine is administered. Codeine gr. 1/4 (0.015 gm.) and atropine gr.  $\frac{1}{250}$  (0.00024 gm.) may usually be employed for the younger, undernourished and poorly developed children. For the older group (5 to 10 years) morphine and scopolamine is useful. The ½ gr. (0.0075 gm.) dose of morphine is never exceeded. A maximum of scopolamine gr. ½00 (0.0003 gm.) serves admirably to diminish secretions and complement the morphine effect by its psychic sedative action. Immediately before use, a 2.5 per cent solution of avertin in amylene hydrate containing 100 mg. per kilogram of body weight is prepared with distilled water. After testing the solution for acidity, an amount equal to 80 mg, per kilogram of body weight is instilled rectally from twenty to thirty minutes prior to the time the bronchographic study is contemplated. If at the end of fifteen to twenty minutes, satisfactory basal narcosis is not obtained, one-half of the remainder of the solution is given. used portion of the drug is utilized if 15 minutes after the second fractional dose the patient still reacts to slight painful stimuli. To diminish the still active pharyngeal and laryngeal reflexes and at the same time assist in eliminating the cough reflex, 1 to 3 c.c. of a 3 per cent metycaine solution is sprayed into the oropharynx under direct vision. Four to six minutes later the patient is anesthetized with nitrous oxide and oxygen, using the carbon dioxide absorption technique.2 Nasal endotracheal intubation is then completed, if necessary under direct laryngoscopy. The distal 3 or 4 inches of the endotracheal tube is lubricated

with 3 per cent metycaine ointment. This not only acts as a lubricating medium, but complements the metycaine spray used to anesthetize the larynx and trachea. The nasal route for intubation is preferred since the tube passed through the small lumen of the nares remains fixed, and the unavoidable shifting which tends to stimulate the cough reflex is eliminated. The head and shoulders of the patient are now elevated approximately 15 degrees and not more than 1 c.c. of metycaine (3 per cent solution) is sprayed during inspiration into the endotracheal tube. After about five minutes anesthetization of the lower half of the trachea, carina, and proximal portions of the primary bronchi is complete. Anesthesia with nitrous oxide and oxygen is again induced. The patient is placed in the optimum position for the instillation of the contrast medium and the technical details for exposing the x-ray plates are completed. To prevent distortion of the plates by respiratory movements,



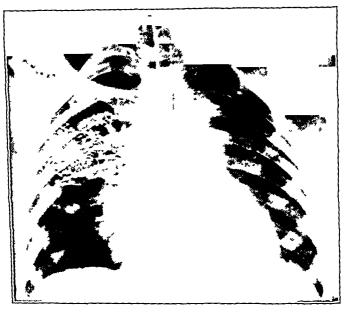
Fig. 1.—Bronchogram made by injecting lipiodol directly into the endotracheal tube, turning patient first to one side and then to the other. After the left side was filled, the movement of the endotracheal tube while changing the position of the child caused a cough which forced the lipiodol into the alveoli of the left upper lobe. By waiting a little longer for the metycaine to take affect the right side was successfully filled.

cessation of breathing is produced for the time required to complete the necessary bronchograms. This may be conveniently accomplished by rapid oxygenation and distention of the lungs immediately following deep nitrous oxide and oxygen anesthesia.

Immediately following the completion of the bronchograms removal of the major portion of the lipiodol is accomplished by means of a simple suction device. (Figs. 2 and 3.) By removing much of the lipiodol, subsequent coughing and the dissemination of infection to healthy portions of the lung parenchyma are minimized. Such suction may likewise be accomplished before the lipiodol is injected to remove excessive secretions

present Obstruction to the contrast medium entering the smaller respiratory passages is thereby largely eliminated.

After this study was complete, a report was published which originated at Guy's Hospital, London <sup>3</sup> In it Jacoby and Keats describe a method which employs basal narcosis with rectal avertin followed by open drop inhalation ether anesthesia. They recommend the method for its simplicity. The obvious objections to ether, namely, the harm that may



 $1\,\mathrm{ng}$  2 —Injection of right upper and middle lobes by gravity (The cuff of the endotracheal tube is filled with lipiodol instead of air)



Tip 3-Same as Fig. 2 after removal of liplodol by aspiration. Oil remains only in the bronchiectatic pockets.

result from its use for patients with existing pulmonary pathology and the dangers from fire and explosions in the x-ray room are not considered of enough importance to constitute a contraindication. They admit the safety and advantages of nitrous oxide-oxygen inhalation anesthesia but claim the technique for its use is too complicated. Our experience does not agree with the latter observation. The method described has not been found particularly complicated for one who has mastered the rather simple exercise of tracheal intubation. The safety with nitrous oxide as compared with ether far outweighs the added inconvenience.

Before instilling the lipiodol, certain anatomical features must be considered. In the normal individual the right main bronchus is almost a continuation of the trachea so that a straight instrument passed directly down the trachea will enter the right lung. If the instrument has sufficient flexibility and is passed farther, it will enter the lower lobe. The right middle lobe bronchus is given off anteriorly, and the right upper lobe bronchus is given off laterally. On the left side the left lower lobe bronchus is a direct continuation of the main bronchus. The left upper lobe bronchus is given off anteriorly.

The measurements of the bronchial tree are also of importance and are shown in the following table taken from Brunings and Albrecht.4

LENGTH IN CM. OF	CHILD 10 YR.	INFANT
Trachea	7	4.0
Right main bronchus	1	0.5
Left main bronchus	3	1.5
Right stem bronchus	2	1.0
Left stem bronchus	1	0.5
Upper teeth to trachea	10	8.0
Upper teeth to carina	17	12.0
Upper teeth to right lower lobe bronchus	20	13.5
Upper teeth to left lower lobe bronchus	21	14.0

The easiest method of instilling lipiodol and the one used most often is that by which the oil is injected directly into the tracheal tube (Fig. 1). This must be done slowly, for, if too much is instilled at one time, it will close the lumen of the tube temporarily and produce obstruction with evanosis and coughing. While the oil is being injected, the head and shoulders of the child are slightly elevated and the body is turned so that the lung to be visualized is somewhat dependent. The lipiodol will then enter the lower lobe. If either of the upper lobes or the middle lobe are to be filled, the patient is placed in that position which will permit the oil to flow in the desired direction. For instance, if the right middle lobe is to be filled, the child is placed on his right side with head and shoulders slightly elevated while the oil is being introduced. After the oil has reached the right main bronchus (about one minute), the position is changed to the horizontal and the body rotated so that it is about three-quarters prone. This permits the oil to gravitate into the middle lobe. If the right upper lobe is to be examined (Fig. 2), the

initial introduction is the same, but, when the oil reaches the main bronchus, the head and shoulders are lowered below the pelvis to allow the oil to flow into the upper lobe. The left upper lobe is filled in a similar manner but with the child on the left side.

Obviously this method is not entirely exact and more than the desired area may often be filled, but it suffices in most cases. When a more accurate localization is required, the oil may be instilled through a No. 10 F whistle-tipped ureteral catheter. Such a catheter, graduated in centimeters, is passed to the desired part of the lung through the tracheal tube. This differs materially from the method used in adults by Goldman and Adams.5 The Thompson bronchial eatheter which they use would block the airway if passed through a tracheal tube in a child. A large ureteral catheter is essential since a smaller one offers too much obstruction to the passage of the unheated oil. The catheter can be bent at the end so that it may be made to enter either lung simply by rotating it and may even be made to enter a branch bronchus. Without fluoroscopic control, however, it is not always possible to be sure that a branch bronchus is entered, and it is much more difficult than the similar insertion of a Thompson catheter. The catheter is rotated so that it enters the desired main bronchus and is inserted the requisite distance for the tip to reach just beyond the point where the branch bronchus to be filled leaves the main bronchus. The child is then put directly in the position which will permit filling of the bronchus by gravity, and the oil is injected. To inject the oil a Luer Lok syringe with needle of sufficiently large caliber to fit the lumen of the catheter quite snugly is used. The injection of the unheated oil requires considerable force, and the leaks around the needle and catheter must be minimized. Heated oil gravitates into the alveoli quickly and does not outline the bronchus satisfactorily. The amount of lipiodol used varies with the size of the child and the extent of the bronchogram. As much as 5 c.c. has been needed for one lobe in a child of 3 years but seldom more than 10 e.e. for an entire lung in a child of 14 years. The instillation of too much oil is of little concern since it is always removed with a suction after the films have been exposed.

In a patient who has undergone lobectomy or pneumonectomy, the relation of main bronchus and trachea is changed so that the main bronchus of the side operated upon is more in line with the trachea and a straight tube will enter that side without guidance. If the right side has been operated upon, it may require considerable manipulation to get the catheter into the left lung. Fig. 4 is the bronchogram of a child who had a collapse of the left upper lobe and a lobectomy of the left lower lobe, the conditions being independent of each other. Lipiodol was injected through a straight fiber tube which is seen passing directly to the left side.

Coughing must be avoided as it tends to blow the lipiodol out into the alveoli, and the value of the picture for diagnosis is impaired (Fig. 1). After the tracheal tube is inserted, five minutes should be allowed for the anesthetic to take effect. The metycaine introduced through the tube should anesthetize the bronchial mucosa, but, if coughing occurs when the catheter is inserted, more metycaine should be injected through it to place the anesthetic directly on the bronchial mucosa. After the oil is injected through the catheter, it is better to remove the catheter before changing the position of the child. Movement of the catheter incident to manipulation of the patient may cause cough even when the bronchus seems well anesthetized.



Fig. 1.—Straight catheter passing directly to bronchus of operated side. In this instance the lower lobe had been removed and the upper lobe collapsed.

The use of a combination x-ray table and fluoroscope would greatly simplify the whole procedure as both could be used without shifting the patient, thus permitting greater accuracy in placing the catheter and filling the bronchus. When the patient is fluoroscoped on one apparatus and then shifted to another for exposure of the film, the procedure is not nearly as satisfactory. It is better to keep the child on one table and estimate the position of the catheter and the amount of oil required using the method described above, than to move the patient from one table to another.

The use of this method for more than a year indicates that it is a safe procedure and without sequelae of any consequence. In only one in-

stance was there any unfavorable reaction. This was a temperature rise to 101° F, accompanied by a few râles in the chest the day after The fever and chest signs had entirely disappeared the bronchography. following day.

## SUMMARY

Methods commonly employed to complete bronchograms for children utilize local anesthesia in the conscious patient. Such procedures are not without danger, and good results are not always obtained. As a substitute method, a technique is described which utilizes inhalation anesthesia with nitrous oxide-oxygen, after basal narcosis with avertin in amylene hydrate and the application of 3 per cent metycaine solution to mucous membranes.

The method permits the accurate introduction of the contrast medium by way of an endotracheal tube and the removal of most of it after the completion of bronchograms.

Results after more than one year's trial indicate that the method is relatively safe, pleasant for the patients, and time saving.

The results with this procedure for completing bronchographic studies for children have been more satisfactory than with any other technique employed.

We take this opportunity to express our thanks to Miss Violet Vernon, formerly of the Bellevue Hospital x-ray department, for her helpful suggestions and valuable assistance.

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# PECTIN-AGAR DIETS IN THE TREATMENT OF BACILLARY DYSENTERY OF INFANTS AND CHILDREN

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A CONTINUATION at the James Whitcomb Riley Hospital for Children of the use of the pectin-agar dextrimaltose product developed by several of us' has made it possible to study the cases of infantile diarrhea admitted to the hospital during the past three years. The high incidence of bacillary dysentery in this series seemed to offer an opportunity to report the use of this new dietary treatment in the type of case which must be considered as giving the crucial test for the efficacy of any therapy for diarrhea.

Much has appeared in the foreign literature on the use of the raw apple diet and apple powder in the treatment of diarrheal conditions of various types, but there have been comparatively few articles dealing with the use of this dietary treatment in infectious diarrhea. reported success in all but one case of 15 dysentery and dysentery-like cases in children from 2 to 10 years of age, while Wolff<sup>3</sup> observed 5 cases of true dysentery with innumerable mucous stools that showed excellent response to the apple therapy in twenty-four hours with decrease in tenesmus and fever, but the improvement was accompanied by a rapid loss in weight. Schreiber4 and Mouzon5 observed that the apple diet acted favorably on dysentery due to Flexner and Hiss-Y bacillus. Heisler. Malmberg, and Earnshaws obtained excellent results in cases of epidemic dysentery while Hartwich reported good results in 19 dysentery cases, 17 being of the Sonne type. Schlesinger<sup>10</sup> reported that patients severely ill with bacillary dysentery seemed to recover more rapidly with the apple diet than did other similar eases treated by the usual methods. However, he felt the patient's recovery was no guarantee that the dysentery bacillus had disappeared from the stools. Skinner,11 in reporting an outbreak of epidemic dysentery in which the diplobacillus was thought to be the pathogenic organism, stated that the apple diet was not specific in any of these cases, but he felt that the marked improvement noted in some of the eases at the termination of the apple diet might indicate a use for this treatment as an occasional complete change of food, thus disturbing the habitat to which the organisms of the bowel were accustomed. In a report of 100 cases of acute dysentery in infants and children under 2 years of age in which the comparative values of human milk, protein milk, buttermilk, a earbohydrate diet and the Moro-Heisler apple diet were given, Sabri and co-

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workers<sup>12</sup> gave the results from the use of the apple or apple powder as being satisfactory but concluded, "Bacillary dysentery is a self-limited disease in which recovery depends upon the development of immunity on the part of the body. Until such immunity has developed the disease will continue its course irrespective of the character of the diet." Smith and Fried<sup>13</sup> observed that none of their dysentery cases treated with the apple diet showed any permanent improvement, but the level of feeding used by these workers in their cases was much lower than that generally advocated for the best results.

While many of these report good results in controlling the diarrhea, the low caloric value of these feedings, the difficulty in feeding the large amounts of apple necessary, the marked weight losses encountered, the difficulty in obtaining desirable fruit, and the trouble repeatedly reported in returning the patients to the normal diet without recurrences of symptoms were definite disadvantages to the apple therapy. It was also felt that the apple diet left something to be desired in producing formed stools.

The pectin-agar preparation was developed in an attempt to overcome the disadvantages of the raw fruit diets and at the same time to retain the good points and to eliminate the necessity of starvation which has always been a basic principle in all types of diarrheal therapy. Influenced by the experimental and clinical work of Malyoth, <sup>14</sup> Bauman, <sup>15</sup> and others showing that pectin and cellulose were the active agents in the apple therapy, a combination of pectin and agar-agar plus dextrimaltose was devised. Although the proportions have been changed several times the product as used the last 3 years was essentially:

Pectin	6.3%			
Agar-agar	4.3%			
Dextrimaltose	89.4%			

These are mixed together in a powder,\* which is used in the milk for the feedings of the infant or child suffering the diarrheal symptoms.

## METHOD

Two basic forms of feedings have been found very practical. A fluid form which is used for the nurslings or for gavage purposes is made in the proportion of 1 cup of the pectin-agar powder to 24 ounces of milk, while for the older child who is spoon fed, the more concentrated combination of 1 cup of the powder to 16 ounces of milk is used. The milk is added slowly to the powder and the combination cooked in a double boiler 10 to 15 minutes with occasional stirring. The more fluid form is placed in nursing bottles in the quantity desired for each feeding. When cold, this forms a soft gel which upon reheating and shaking will break down into a smooth thick liquid and can be fed

<sup>\*</sup>Kindly furnished by Mead Johnson and Company, Evansville, Ind.

through a nipple with an enlarged opening. The infants take the feedings as readily as do the older children. However, we have found that it is sometimes necessary to add flavoring such as chocolate, vanilla, or peppermint, or sliced bananas, banana powder, or various colorings to overcome the objections which were sometimes encountered with the older children. Some from this older group seemed to prefer the feedings warm, while others took them more readily if chilled or even frozen. During the first few years of the use of this product, while we were uncertain as to the extent of the therapeutic action of this material, we made the feedings with water, then very dilute milk mixtures, and later skimmed milk. However, during the last three years one-half skimmed and even whole milk have been used with equal success.

The peetin-agar feedings were ordered for the infants upon admission, and no starvation period was used. No other food was given by mouth except glucose water which was offered ad libitum. Complete bedside records were kept for each patient.\* Daily weights, temperatures, amounts of fluids taken, frequencies and types of vomiting were charted. The type of formula, method of administration, amount of each feeding taken and how the child took the feeding, as well as complete stool records giving the number, consistency, quantity, color and the mucus, pus and blood content were kept. Supportive therapy was given as deemed advisable. To combat the dehydration which was present in some degree in practically every ease in this series, fluids were given by mouth. However, in many cases insufficient amounts were taken or retained and when the normal urinary output could not be restored, parenteral routes were used. Glucose alternating with saline was given intravenously and in some cases subcutaneously; and, when more normal circulatory volume had been reestablished, one or two and in the severe cases even four or more small blood transfusions were given. anorexia was encountered in many of these severely toxic patients, it was often necessary to give the feedings by gavage. In cases with vomiting as a disturbing factor, the thick consistency of the pectin-agar feedings tended in the majority of cases to reduce the regurgitations; however, if the vomiting continued, it was sometimes necessary to give very frequent feedings of a more concentrated formula; in some very persistent eases the feedings were withheld for 12 to 18 hours and then resumed.

Proctoscopic examinations were made on every case possible. The rectum was flushed with physiologic saline solution, and a smear was taken directly from the bowel wall for examination. Stool specimens were taken on three successive days for culture, and all specimens were examined and cultured promptly after collection. During the summer of 1936 agglutination tests for the dysentery group were done routinely on admission and just before discharge; during the other two years agglutination tests were done only for the patients who were suspected of

<sup>&</sup>quot;It is a pleasure to acknowledge the generous assistance of Nell Kolb, R.N.

TABLE I
RESULTS FROM PECTIN-AGAR TREATMENT

	1936   1937				1938		
{		BACIL-	INFEC-   BACIL-		INFEC-   BACIL-		
	INFEC-	LVLA.	TIOUS	LARY	TIOUS	LARY	
{	GASTRO-	DYS-	GASTRO-	DYS-	GASTRO-	prs-	
	ENTERITIS	ENTERY	ENTERITIS		ENTERITIS		
NUMBER OF CASES	6	19	17	15	4	18	
NUMBER OF DEATHS		6	5	8		2	
RESULTS OF RECOVERED	AUPDACEC	AVEDAGES	LYFRAGES	AVERAGES	AVERAGES	AVERAGES	
CASES			1	I	i	(	
No. days illness prior to treatment	7.5	7.2	21.5	8.9	21.7	7.3	
No. of stools per day prior to treatment	9.9	14.2	9.8	8.5	9.0	12.8	
Age in months	24.7	19.8	10.6	26.1	7.2	19.6	
Temperature on admis-	100.7	101.5	99.6	101.2	100.8	101.6	
sion.	101.7	103.3	102.0	104.0	101.0	103.3	
Highest temperature		16.0	6.3	11.5	4.3	8.7	
No. days temperatures over 99.8°	3.5	10.0	{ 0.5	11.0	4.0	0.,	
No. days in hospital	14.8	22.2	25.4	30.0	13.0	17.2	
No. days on straight treatment	6.8	12.9	7.9	11.3	6.5	11.2	
No. days on transitional treatment	4.2	14.8	4.8	10.6	4.0	4.0	
Total gain in ounces or straight treatment	7.5	1.3	9.3	3.4	16.3	7.2	
Total gain on transition al treatment, in oz.	4.5	7.8	6.6	2.8	2.8	4.0	
No. calories per pound per day on straigh treatment	36.1	33.0	52.4	43.0	49.0	50,3	
No. calories per pound per day on transi tional treatment	44.8	47.1	57.2	47.0	*	*	
No. days stools were lic	1	13.0	6.6	12.4	3.0	7.5	
No. days until first sor stools appeared	{	0.7	0.9	1.4	1.0	1.4	
No. stools per day o straight treatment	n 3.9	5.2	5,0	5.3	5.9	5.4	
Per cent liquid stools of straight treatment	1	31.7	36.0	51.5	41.8	33.0	
No. stools per day of transitional tree ment	t-	4.1	3.6	2.9	2.1	3.8	
Per cent liquid stools of transitional tres ment	on 0	12.2	8.1	21.2	0	S.7	
No. days mucus was preent	1		6,4	13,8	1.5	7.5	
No. days pus was pr ent		12.4	1,3	5.5	1.0	1.6	
No. days blood was pr ent	es- 3.5	12.1	2.3	G.S	0	3.8	
Per cent recurrences	16.7	1 15.4	8.3	0	-		
Per cent mortality	0	31.6	20.1		-\- <del>"</del>	11.1	
*Diets were so diversified accurate records were not kept.							

having bacillary dysentery but from whom the specific organism had not been isolated. Very careful morphologic, cultural, and serologic studies for the identification of suspicious organisms were made. Diagnosis was based on positive bacterial findings in 68.5 per cent of the cases here reported. Although it is realized that any attempt to classify the cases of diarrhea, other than those with positive bacterial findings, is at best a very arbitrary thing, it seemed that the cases which were probably of dysenteric origin but failed to give positive bacterial findings should be included in this report. Therefore, we have designated those cases with history of contact with dysentery, with bloody mucoid stools, with positive proctoscopic findings, and other typical clinical symptoms but failing to give positive bacterial findings as infectious gastroenteritis probably of dysenteric origin.

When it was felt that the improvement in the child's condition warranted a return to the normal formula, the amount of peetin-agar powder was progressively reduced for a few days with the subsequent resumption of the standard feeding routine. The older children were given a transitional diet consisting of two or three feedings of the pectin-agar gel with a modified soft diet fairly high in protein and containing only the bland fruits and very little vegetable material. After a few days, the peetin-agar feedings were discontinued and the regular diet resumed.

## RESULTS

Table I gives a summary of the results from the treatment of 52 cases of specific dysentery and 27 cases of infectious gastroenteritis which were probably dysentery. In the various groups soft stools appeared on the average from seven to thirty-four hours after the pectin-agar feedings were first given with an abrupt reduction in the average total number of evacuations daily. In the milder cases the response was often rather spectacular with soft stools appearing within a few hours after the first pectin-agar therapy, but in the more severe and toxic cases, while the appearance of the first soft stools was fairly prompt (twenty-four to seventy-two hours), the general improvement was often slow although steady. Children admitted before the extreme moribund symptoms had developed and treated for at least forty-eight hours showed definite improvement in 73.4 per cent, with reduction in temperatures, improvement in form and contents of the stools, and definite and often very marked decrease in tenesmus and general discomfort.

The average caloric intake per pound ranged from 33 to 52.4 calories and weight gains resulted in each group. The periods of straight treatment averaged from 6.5 to 12.9 days and the transitional diet was given from 4.0 to 14.8 days. The mortality ranged from 0 in gastroenteritis groups of 1936 and 1938 to the high of 53.3 per cent in the bacillary dysentery group of 1937. The mortality for the entire series was 26.6 per cent. The median age of all the patients reported was 10 months.

TABLE II								
Cases of Diarrhea	TREATED	WITH TH	THE REE	PECTIN-AGAR SUMMERS	FEEDINGS	During	THE	Last

TYPE	1936	1937	1938	JATOT		
Bacillary Dysentery	19	15	18	52		
Flexner	18	15	11	44		
Shiga	1	}	c	1 0		
Sonne	(	{	1	li		
Hiss-Y Infectious Gastroenteritis	6	17	4	27		
Parenteral	3	15	16	34		
Dietary	1	5	4	10		
Miscellaneous		4	$\frac{1}{3}$	1 7		
Total of all cases 130						

Table II is the summary of all the cases of diarrhea treated during the three years. Our main interest here is in reporting the infectious type of cases, but we feel it should be mentioned also that in the noninfectious cases this therapy has proved extremely successful.

## OBSERVATIONS AND DISCUSSIONS

This report covers a series of unusually severe hospitalized cases of infectious diarrhea. The infants were referred to the hospital from all parts of the state, and often considerable time elapsed between the onset of the symptoms and the time the treatment was started. Patients admitted in comatose state, in whom the moribund course was not altered in spite of all therapeutic efforts and who died within forty-eight hours after admission to the hospital, are not included in this series.

All variations in symptoms were observed, ranging from 7 patients with blood and mucus in their stools, but with little or no fever and giving the appearance of being quite well, to the majority of the cases at the other extreme with marked prostration, high fever, rapid and marked dehydration, extreme emaciation, disturbed consciousness, and, in several cases, death within forty-eight hours after the onset of the diarrhea. Complications were encountered frequently, particularly in the 1937 series. Of the cases of bacillary dysentery and of infectious gastroenteritis treated during the summer of 1937, 81 per cent of the cases had complicating conditions, with otitis media, bronchopneumonia, pertussis, and pyclitis encountered most frequently. When one considers that these infants were not only suffering from the serious gastrointestinal disturbance, but also from one and usually two complications and that the average age for the two groups was 10.6 and 26.1 months, one is not surprised at the mortality rates of 29.4 and 53.3 per cent.

Since the hospital is a state institution for charity cases, the patients came from homes of rather low economic status, and the incidence of malnutrition, even to marasmus with emaciation to almost unbelievable states, was quite high. In those children having poor previous nourishment, the disease was not only severe, but often it developed into a

rather chronic state with frequent complications and necessitating long periods of hospitalization. Ten such cases were encountered in this series with periods of hospitalization ranging from 57 to 87 days.

Of the cases treated, the youngest was 1 month and oldest 7 years, with the age distribution as follows: 1 child of 7 years, 1 of 6 years, 2 of 4 years, 14 between 2 and 3 years, 20 between 1 and 2 years, and the remaining 41 infants being less than 1 year old, with the median age of 10 months for the whole group.



Fig. 1.—Stool resulting from the pectin-agar feedings, showing the peculiar soft consistency.

The stools resulting from this therapy have a peculiar soft consistency (Fig. 1). We wish to emphasize that with this type of diet a great deal of indigestible bulk should be given to make four or more large and This is why it seems better in interpreting the bulky stools daily. response to this therapy, to be guided more by the consistency, whether it is soft or liquid, and the stool contents, whether pus, blood, or mucus is present, rather than by the number or volume of the stools. prompt appearance of soft stools and the decrease in number of liquid evacuations are of utmost importance in checking the excessive loss of fluids from the already dehydrated infant. In the dysentery cases the stools gave the characteristic foul odor with varying amounts of blood, pus, and mucus. In some stools blood occurred in small streaks, and in others practically nothing but blood and mucus was present. In the stools of the patients fed pectin-agar, the disappearance of the blood, pus, and mucus was measurably more prompt than in the stools of comparable patients treated with other diets, including protein milk, acid milk, and the raw apple.

The rationale of giving a high carbohydrate milk feeding may be questioned by some as it was by us. We have found that the carbohydrate tolerance for our mixture is surprisingly high, and, when it is incorporated in the milk to supply the protein, our patients, in spite of the severity of the disease, have not only maintained their weights

but have shown weight gains. In our original study no milk was used; however experience has taught us that high concentrations are equally well tolerated even in severe specific dysenteries. Special feedings devised for a few extremely marasmic infants incorporating powdered milk, egg yolk, and vitamin concentrates to give caloric values as high as 100 calories per pound have been used successfully and apparently have saved the lives of some who were getting progressively worse on other diets.

The addition of the pectin-agar powder to the fresh milk brings about a precipitation of the milk in an extremely fine grained curd, which probably tends to increase the digestibility of the milk. This reaction was described by Joseph<sup>16</sup> as apparently due to some specific property of the colloidally dispersed pectin, either from a process of sensitization or through the removal of calcium from the caseinate complex by the pectin, by adsorption or actual chemical combination. A similar reaction has been observed when apple powder is added to milk.<sup>17</sup>

During the 1936 series recurrences of the symptoms during or shortly after the patients had been given the transition diet were encountered in 16.7 to 15.4 per cent of the cases. However, during the 1937 and 1938 series, the recurrences were very rare. We have come to realize that in states of intestinal disturbances, such as encountered in these severely ill infants, the treatment is not a matter of two or three days but of a week or more. Our return to the normal regime has been postponed until the child was definitely improved, and then a more gradual transition is used.

In this series of 79 cases, only 5 infants were encountered who because of excessive vomiting, extreme distention, or failure to respond to the pectin-agar therapy as well as expected were changed to other types of feedings. Three of these patients showed improvement on the changed feedings, and of the other two, one continued to vomit all feedings and the other showed no change in degree of distention before death.

The response to this type of feeding is measurably more prompt and complete than that observed in similar cases treated by other dietary means. The results from feeding the apple diet to a group of infants and children suffering from various types of diarrhea were compared with the results from a similar group given the peetin-agar feedings. It was found that when the raw scraped apple was fed, longer periods of treatment and transition were required; recurrences were more frequent; the appearance of soft stools, the cessation of liquid evacuations, and the disappearance of blood, pus, and mucus were not as prompt as in the group fed peetin-agar; the feedings were not as well taken, and there was a weight loss, as compared with a gain in weight observed in the peetin-agar group. Again in a comparison of the results from the use of lactic acid milk and peetin-agar in treatment of cases of bacillary dysentery, it was found that patients responded more quickly to the peetin-agar feedings and required a shorter period of treatment, that 41 per cent

liquid stools occurred with the lactic acid milk as compared with 28 per cent with the pectin-agar, and that liquid stools persisted in the lactic acid group for 16.2 days as compared with 8.9 days in the pectinagar group.

Speculation as to the mode of action of the pectin and of the agar in the treatment of diarrheas has been rather widespread during the last few years. Scheer<sup>10</sup> used agar milk combinations for diarrhea and suggested that the agar acts as a colloidal disperser of the milk protein, aiding in the ease of digestion, acts on the acid base balance, and aids in controlling the water balance. These ideas were also endorsed by Calvo.<sup>20</sup> Frias<sup>21</sup> considered the action more on the motility of the gastrointestinal tract with a regulating action neither laxative nor astringent. Little can be added to the summary of Manville and collaborators<sup>22</sup> on the various actions of pectin. They considered as important factors pectin's great absorptive capacity for bacteria and toxins, its ability to take up large quantities of fluids and thus provide bulk in the intestines, the buffer action, the action as a protective colloid, and the detoxifying action of the galacturonic acid formed by the breakdown of the pectin.

Since the bactericidal action of pectin has been demonstrated to be specific for a metal pectin product<sup>23</sup> and not a property of pectin per se, it does not seem probable that this bactericidal action has any therapeutic effect in the gastrointestinal tract. Work which was completed recently in this laboratory showing that in dogs pectin has a prophylactic as well as curative action for experimental ulcers resulting from administration of cinchophen<sup>24</sup> seems to offer more evidence to justify the use of this therapy. The action of the pectin in this work was felt to be, in part at least, a mucus-sparing or a protein-sparing action probably due to the uronic acid content of the pectin, which acted in a manner similar to that of glueuronic acid.

The total action of this pectin-agar combination is not completely understood, but it would seem to be a combination of the physicochemical and mechanical actions of the materials. Since the agar and pectin make a gel which passes through the gastrointestinal tract as such, liquid stools, in most instances, are a physical impossibility. The formation of the gelatinous mass and the breakdown of the pectin with the liberation of galacturonic acid, the absorbing, emulsifying, detoxifying, and diverse other actions of pectin and its split products result in a cooperative action to give the total therapeutic effect.

The use of this high caloric therapy for diarrhea fits in with the modern method of treating typhoid fever since both feed the patient rather than starve him and strive to maintain as good nutritional state as possible. It seems that this peetin-agar therapy is particularly suitable for treatment of these severe infectious diarrheas since it not only has a therapeutic action on the diarrheal symptoms, but also offers a well-balanced, nourishing, and easily digested food which tends to keep up the infant's resistance until the time when the natural immunity can

be developed. This diet has proved very practical and workable in that its method of preparation is simple; the average child takes the feedings quite readily; and it is made from the stable standard powder which is not subject to seasonal supply.

## SUMMARY

A series of 52 cases of bacillary dysentery and 27 cases of infectious gastroenteritis, probably dysentery, in infants and children treated with the pectin-agar dextrimaltose combination is reported.

There was a definite and quick response with soft stools within an average of thirty-four hours and a gradual and steady improvement in 73.4 per cent of the cases.

The caloric intake averaged from 33 to 52.4 calories per pound per day, and average weight gains were observed in every group.

The mode of action of this therapy is probably both physicochemical and mechanical, with the uronic acids playing an important part.

The diet is peculiarly suitable for infectious cases, since besides having a definite therapeutic action, it is high in calories, well balanced, and casily assimilated, and it maintains nutrition while the body has a chance to develop the necessary immunity. It is easily prepared, very readily taken, available, standardized, and safe. Our experience continues to confirm our early observations that this pectin-agar diet very definitely more quickly and completely produces formed stools with fewer recurrences than other accepted methods, including the apple diet.

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# CONGENITAL CARCINOMA OF THE THYMUS WITH EXTENSIVE GENERALIZED METASTASES

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PRIMARY carcinoma of the thymus is not a common finding and still less common is congenital primary carcinoma of the thymus. The literature on the subject is summarized in an extensive review by Crosby, who reports 44 cases of carcinoma collected from the literature up to 1932. In 1936 Slesinger brought the total number, including one case of his own, to 53 Additional cases have been reported by McDonald, Decker, Kahr, and Goyle, Vasudevan and Krishnaswamy.

The majority of these reports are those of adults who presented the typical findings of tumor of the thymus upon clinical examination. Bedford described the only ease that involved a newborn infant, a child who lived 17 days. There was a generalized cruption on the skin of moderate degree clinically suggestive of syphils. The blood Wassermann, however, was negative on two occasions. A history of repeated attacks of dyspnea, together with physical and x-ray examination of the chest, made possible a diagnosis of enlarged thymus. At autopsy a large thymic carcinoma was found. The tumor was firmly adherent to the lungs, and microscopic examination revealed numerous metastases to the lungs, liver, bone, and skin.

The present case, observed at Mount Sinai Hospital, Cleveland, is similar in many respects to that of Bedford, the extent of the metastases, however, is much greater Both presented essentially the same clinical pictures in newborn infants, and syphilis was suspected and looked for in each. In both, at autopsy a highly malignant carcinoma of the thymus was found, together with extensive metastases to other organs

#### CASE REPORT

The mother was a 29 year old primipara, who was admitted in active labor. She gave a history of congenital syphilis, with an undetermined amount of treatment administered at various times. Her slide test for syphilis at the time of delivery was two plus diagnostic and four plus exclusion. The only other point of interest was the habitual use of large amounts of a phenolphthalein laxative.

Shortly after admission she gave birth to a full term male child weighing 2,860 gm. The delivery was normal and unattended by any appreciable difficulties. A striking generalized eruption involving all portions of the skin of the child was noted immediately (Fig. 1). The lesions were variable in appearance; some were merely small ecchymotic flecks, while others were macular, papular, vesicular, or even pustular. A few of the more prominent lesions appeared hemorrhagic. The lesions varied from 1 to 8 mm in diameter. On several occasions the temperature

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rose to 100° F., but no marked elevation was noted at any time. There was a steady loss of weight with death occurring after seven days, apparently due to increasing respiratory distress. During this period, the skin lesions changed somewhat; many steadily enlarging, breaking down, and becoming crusted over, while at the same time other new ones appeared.



Fig 1—Photograph showing generalized eruption noted at birth. Macular, pupular and resicular lesions present everywhere varying from 1 to 8 mm. in

The laboratory reports of interest were as follows:

Shide test for syphilis on umbilical cord blood and on baby's blood was negative in both the diagnostic and exclusion tests.

Blood counts showed red blood cells, 4,740,000, white blood cells, 18,500, with the following differential count mature polymorphonuclear neutrophiles, 37 per cent; juvenile cells, 26 per cent; metamyelocytes, 10 per cent; myelocytes, 5 per cent; myeloblasts, 1 per cent, eosinophiles, 3 per cent, monocytes, 2 per cent; and lymphocytes, 16 per cent

Bleeding time was ½ minute, clotting time, 3 minutes, and the icterus index, 31.

Numerous smears of the skin lesions stained by the Fontana method showed no spirochetes. Gram stains of skin lesions demonstrated occasional gram positive cocci. There was also a slight growth of Staphylococcus aureus upon culture of

material from a lesion

The various clinical impressions were recorded as follows: Third generation syphilis; phenolphthalein rash (due to excessive use by the mother); a blood dyscrasia; and a widespiead metastasizing tumor such as a Kaposi sarcoma. However, no satisfactory final diagnosis was made clinically.

## 1utopsy

Shin.—There is a generalized cruption with innumerable rounded and irregularly shaped lesions, varying in size from 1 mm to 8 mm in diameter. These lesions are extremely variable in appearance, ranging from single small intracutaneous flecks, to large vesicular, pustular or crusted areas. Some sites contain grayish or reddish brown fluid material. The lesions are numerous and most striking on the soles of the feet.

Mouth - Mucous membranes show a number of small, apparently ulcerating lesions similar to those in the skin

Heart.—The only appreciable gross abnormality is a small rounded reddish subepicardial area which is at the base of the right ventricle and extends into the underlying myocardium

Lungs present a striking picture. They are larger and firmer than average. Many bleblike are is, variable in size and discolored gray and deep red, are seen through the pleura and on section of parenchyma. In numerous places there are apparently necrotic areas with unbilication or actual defect formation. The entire pulmonary tissue presents a deeply congested, mottled, and dark red appearance.

Pancreas is of average size and shows numerous well defined grayish white areas of fine architecture, suggesting granulomas or tumor tissue.

Thymus is moderately enlarged. There is no recognizable thymic structure Tissue is firm and on section is gray with numerous areas that suggest necrosis or suppuration. Small granuloma like nodules are noted in places. Regional structures are not adherent to the thymus, and there is no apparent extension of the abnormal thymic tissue to lungs or mediastinal structures.

Mesenteric Lymph Nodes—Several slightly enlarged, round, discrete, grayish fleshy nodes are present

The remaining organs, including brain, pituitary, and pineal gland, show no gross lesions

# Microscopic Description

Micro-copic examination of the various tissues shows involvement of epicardium, lung, liver, spleen, pancreas, large intestine, thymus, lymph nodes, brain, skin, and bone marrow. The lesions are essentially of two types.

The first type, seen in the epicardium, liver, spleen and bone marrow, suggests an infiltrative or possibly a granulomatous process rather than a tumor. The in volved tissue in these organs appears to be made up of large irregularly shaped cells, in loo-ely bound arrangement. Nuclei are rounded and vesicular and show an occasional chromatin knot. Cytoplasm is pale staining. Rare mitotic figures are

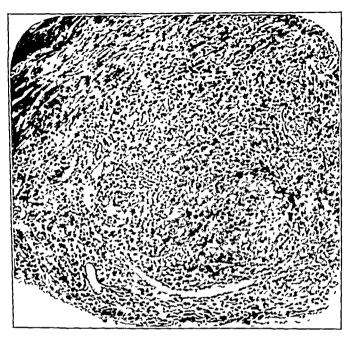


Fig. 2.—Photomicrograph of epicardium Metastasis showing a granulomatous appearance with a small area of central hemorrhage.

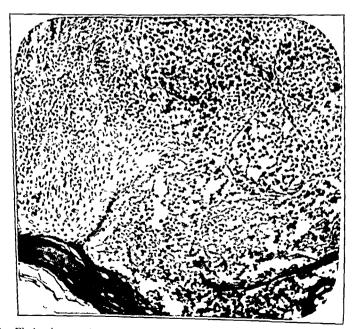


Fig. 3 —Photomicrograph of skin Metastitic area with necrosis of tumor and ulceration of epithelium.

noted. There is no evidence of tissue destruction although occasional small areas of hemorrhage are present. The involved epicardium (Fig. 2) shows such a typical lesion.

In the skin the lesions in many areas are more advanced and suggest metastases with necrosis. Here poorly circumscribed rounded nodules are found made up of cells similar in structural and histologic arrangement to that described above. The cells in places extend as small strands into the underlying tissues. The epithelium immediately overlying the nodule frequently appears ulcerated and necrotic (Fig. 3).

The second type of lesion, which definitely suggests tumor, is found in the other involved organs. In the lung, for instance, the greater portion of the tissue is made up of a diffuse sheetlike mass of cells in which the usual lung markings may still be made out. In many areas there is a suggestion of an alveolar arrangement. The cells show a large rounded nucleus and a moderate amount of pale stained cytoplasm. Many cells are polyhedral. In some areas numerous small dilated and engorged blood vessels are present, apparently forming a part of the tumor. Occasional large multinucleated giant cells are present (Fig. 4). In places there is a suggestion of tumor cells within vessel lumina.



Fig. 4 -Photomicrograph of lung Metastasis showing abundant giant cells

The tumor is apparently oldest and furthest advanced in the thymus. The section here shows no recognizable thymic structures. There are numerous small roughly rounded areas in which the tissue appears necrotic. There are also deeply blue stained sites suggesting calcification (Fig. 5). An occasional giant cell is noted regional to the necrotic and the calcified areas. The greater portion of the section is made up of a sheet of tumor tissue with architecture in places vaguely alveolar in appearance. Cells are large, polyhedral and rounded with prominent, rounded, poorly stained nuclei. The cytoplasm is variable in amounts. In places it is abundant, lightly stained and vesicular, whereas in other places there is very

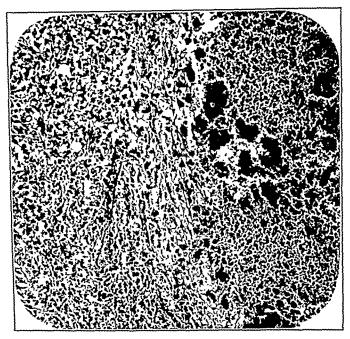


Fig. 5.—Photomicrograph of thymus. Primary tumor showing the diffuse sheet of pleomorphic tumor cells and the regional area of necrosis and calcification.

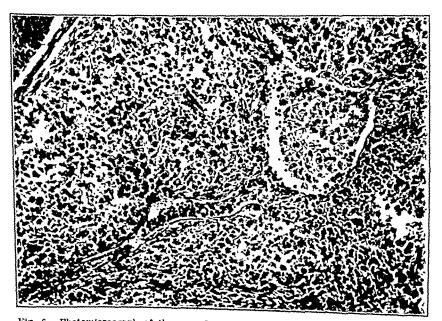


Fig. 6.—Photomicrograph of thymus. Primary tumor with tumor cells invading and distending lymphatic spaces.

little present. Mitosis is noted occasionally. There are areas where the cells appear compact and other sites where the cellular structure is loosely arranged with irregular spaces between the cells. The tumor is separated into poorly defined nodules by septumlike structures made up of spindle cells. Tumor tissue in places apparently fills lymphatic spaces (Fig. 6). At the periphery there are small focal nests of round cells present.

Similar lesions are noted in the pancreas, lymph nodes and liver.

Because of the pleomorphic appearance of the tumor the slides were submitted to Dr. James Ewing, and his comments are as follows: "The structure reminds me strongly of the large cells of thymoma, and this, I think, is the best interpretation. The giant cells recall some of the endotheliomas of lymph nodes which I used to describe. . . . My guess would he thymic carcinoma with metastases in an infant."s

#### COMMENT

The clinical diagnosis of thymic carcinoma is obviously difficult. The most prominent clinical symptoms in the adult are respiratory and circulatory disturbances due to pressure. Hence, dyspnea and evanosis are the most striking features of the disease. In the newborn infant, however, dyspnea and evanosis are usually attributed to other more common causes such as cerebral injury, atelectasis, or congenital heart disease. Supracardiae dullness, which is one of the cardinal signs of this condition in the adult, is not a dependable finding in the newborn.

The extensive congenital lesions of the skin in the case reported here should make one realize that he is dealing with a generalized pathologic process which has also invaded the skin. Once syphilis has been ruled out, one should think of the possibility of metastatic malignancy. Thorough physical and laboratory examinations, including x-rays of the chest and long bones, should be done in the search for the primary lesion.

#### SUMMARY

The second case of congenital primary carcinoma of the thymus with extensive metastases to be recorded in the literature is reported above.

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# SUBCUTANEOUS EMPHYSEMA IN THE NEWBORN INFANT

# CASE REPORT

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R ECENTLY we encountered a most unusual condition in a newborn intant, the rarity of which warrants its reporting.

J. D., the second of twins, was born on April 7, 1938.

H. D, gravida 11, aged 25 years, the mother, was delivered of a stillborn child in 1936. The presentation at that time was a footling breech. The cause of death of the infant was not known.

The last menstrual period of the mother was June 30, 1937, making the expected date of delivery April 14, 1938. Pregnancy progressed normally the first months although the fundus height did seem too great for the period of gestation. On Jan. 7, 1938, an attempt was made without success to diagnose twins. We tried to rotate the breech that was presenting but desisted because of the vertigo which came on immediately. On January 25 the suspicion of twins was confirmed by examination by x-ray. At this time the urine had present a faint trace of albumin. On March 22 the blood pressure was 154/86, weight 166 pounds, height of the fundus 39 cm. The urine showed a marked trace of albumin. Since the patient was so miserable that it was pitiable, an attempt was made to induce labor by medical means on March 30. This was not successful

Labor began on April 6 with a breech presenting. The membranes ruptured spontaneously about three hours after the onset. The first stage lasted approximately 10 hours. During this time pentobarbital (nembutal) gr. 6, and hyoscine gr. 1/100 were given in divided doses. Rectal ether was administered, but very little of it was retained. During part of the second stage, which lasted between forty five minutes and one hour, gas and oxygen were given with contractions.

Under ether anesthesia the breech was delivered spontaneously. Some as sistance was given in the delivering of the shoulders and head. Eleven minutes later the second amniotic sac was ruptured, and the second infant delivered by version and breech extraction. The placenta was delivered by Brandt's maneuver six minutes later.

The first baby, a girl, breathed immediately and cried lustily at birth. The second infant, a boy, made strenuous gasping attempts to breathe. At first he was pink, but soon became cyanotic. While he was attempting to breathe, the intercostal spaces drew in with great force. The fauces and trachea were cleared with a rubber catheter. In a short time it was noticed that the left side of the chest and the left supraclavicular space and neck up to the chin were markedly swollen. The mass in the neck was about the size of half an orange. Crepitation was felt in these areas. Oxygen was administered continuously. Breath sounds were heard over the right chest, but none on the left. A radiogram taken at six hours showed a completely atelectatic left lung.

The baby cried fifty minutes after delivery. Coramin 0.5 c.c. and 10 c.c. of his mother's blood (the latter is a routine procedure) had been given intramuscularly. Oxygen was continued for eighteen hours because, on discontinuing it, cyanosis was noticed. The emphysema was still present, more noticeable if anything. At thirty hours, examination by a ray showed the left lung clear again.

From the Obstetric and Pediatric Services, Memorial Hospital

The emphysema slowly diminished in extent and had disappeared by the fifth day. Except for a slight feeding problem, his progress has been normal. The girl, who weighed 5 pounds 14 ounces at birth, weighed 16% pounds on Jan. 6, 1939; the boy, who weighed 5 pounds 11 ounces at birth, weighed 181/4 pounds on the same date. Incidentally, they won a prize at the county fair.

#### COMMENT

Subcutaneous emphysema is "one of the rarities of medicine from intrinsic causes." The cause in this case, we think, was the violent gasping attempts of the baby to breathe after birth. We think the extremely vigorous attempt to breathe ruptured one of the alveoli, allowing air to escape. The air must have filtered into the mediastinum to have been noticeable in the neck. The attempted external version could hardly have caused the condition, because the time element would make us think a permanent defect would have resulted and a larger area of the lung would probably have been affected. The version and breech extraction were accomplished with no difficulty or trauma. It is possible to cause such a condition by injudiciously inflating the lung mechanically. Such was not the case here, as the emphysema was noticed before oxygen therapy was given.

Slot and Brown<sup>2</sup> have recently reported a case similar to ours and have reviewed the literature. Treatment is the administration of oxygen until the condition rights itself. Puncture of the emphysematous area is not advised because of the danger of infection. It might be possible, however, that in a premature infant the accumulation of air in the neck might suffocate the child because of pressure on the trachea.

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# A BUCCAL OXYGEN-ETHER CATHETER

ROBERT COHEN, M.D. LOUISVILLE, KY.

WHETHER in the home or at the hospital, at some time or other the physician will encounter the problem of giving oxygen, oxygen-carbon dioxide, or oxygen-helium. I wish to present a method of giving these gases which gives the greatest comfort to the patient with the least interference. It is to do away with factors which hinder the normal usages of the nasal passages.

The average physician does not use an oxygen tent readily because of its bulk, transportation problems, and perhaps because of the financial factors. The mask and bag method for the administration of oxygen limits the use of the nose and mouth. An oxygen room would be the ideal thing, but it is impracticable. The use of tanks from which oxygen is made to bubble through water in a wide-mouth stoppered bottle is one of the most popular methods in use today.

On the market today are a variety of metallic tubes to aid in carrying this oxygen to serve the patient. You may encounter in the current surgical supply catalogues the Bullowa nasal tube, the Connel nasal tube, the single nasal tube of Gates, the Gwathmey nasal tube, and the Sanford nasal tubes. In addition small rubber catheters, which are also inserted intranasally, are used in many hospitals.

My criticism of the catheter is that it obstructs the nasal passages. In pneumonia we should have all the respiratory channels free for their physiologic purposes. The rubber catheter gags some patients easily. The types that plug both nares interfere with mucous discharge. The objections to the mask type are that it causes apprehension, does not allow room for sipping fluids or foods, and hinders the patient in calling readily if he needs assistance.

To overcome these criticisms I have devised the buccal catheter. By means of it oxygen is conveyed via the oropharynx to the lungs and leaves the nasal passages free.

This instrument is constructed so as to lie adjacent to the buccal mucous membrane and lateral to the dentogingival area. Only the inner aspect of the instrument, which is the side facing the oral eavity, permits the oxygen to escape. The patient can cry out if he desires and can sip fluids without disrupting the mechanism. Thus it helps satisfy oxygen want, allows the physiologic action of the nasal and pharyngeal passages, keeps the patient as comfortable as humanly possible, and perhaps with less apprehension.

The principle of the buccal catheter and its construction are simple and economical. Two brass tubings \( \frac{1}{16} \) inch in diameter and 4\( \frac{3}{4} \) inches long are so shaped as to be pyriform at one end, the end that is in the oral cavity. Then the portion of the tubing at the lower lip level is bent in an angle of about 110 degrees with the chin base. One inch of tubing is allowed for resting on the chin base under two hooklets from which it may pivot. The final \( \frac{1}{8} \) inch of tubing is bent at right angles to the chin base portion. To this portion rubber tubing is attached to lead to the oxygen. The other end of the tubing is closed. The chin rest has two hooklets on each side, 1\( \frac{1}{4} \) inches apart. These hooklets are raised portions of the zinc or galvanized tin \( \frac{1}{2} \) inch from each other. The chin base is molded to fit the natural curvature of the chin. Five perforations are drilled into the tubing of each pyriform wing on the side that faces the teeth only.

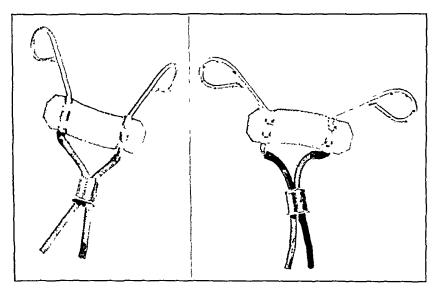


Fig. 1.

Fig. 2.

Fig. 1.—Front view. The ring about the tubing adjusts the abduction of the wings. Fig. 2.—Rear view. This shows the perforations on the pyriform wings which face each other.

To use, raise the lips and slip the pyriform wings between the teeth and the buccal mucous membrane. To adjust for the different widths of mouths encountered slide a ring about both tubings which lead from the arms of a Y glass tube to the buccal catheter. This causes the wings of the catheter to abduct and have more firmness against the cheeks since the right angle portions turn inward. If too firm, the slipping of the ring downward releases the pressure proportionally. Adhesive tape is applied to the ends of the chin base for security

against the skin. However when in the recumbent position it has a tendency to stay in place because of the pressure against the buccal mucous membrane.

This buccal catheter serves another very useful purpose in oral surgery—the giving of ether. In doing tonsil or adenoid operations, the ether hook of the suction and pressure pump can be removed and replaced by attaching it to the buccal catheter. It remains out of the way of a mouth gag very nicely. Thus this catheter serves a dual duty.

The illustrations show the simplicity of this apparatus.

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## THE FUTURE OF AMERICAN PEDIATRICS

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PEDIATRICS is one of the oldest, if not the oldest, of the specialties; its foundations were laid during the Renaissance (1453-1600) by Bagellardus, Metlinger, Phaer, Hieronymous, Sainte Marthe, Glisson, and others. By the twentieth century the pediatrists were recognized as specialists to whom general practitioners referred patients for diagnostic and therapeutic advice, similar to the practice in other specialties. During the present generation, the amount of teaching of children's diseases in the medical schools and the number of pediatric internships in the hospitals have grown tremendously. As a result, the number of pediatrists in the United States rapidly expanded to the present total of 3,383. The specialty soon lost its consultative function and became general practice with an age limit of puberty.2 During the last decade the introduction of preventive measures, many of them developed by pediatrists, has completed the metamorphosis, so that pediatries today is more of a division of public health and preventive medicine than a clinical specialty.

This change in pediatrics has been recognized by the federal government, and the Technical Committee on Medical Care of the Interdepartmental Committee to Coordinate Health and Welfare Activities on July 18, 1938, recommended to the National Health Conference<sup>3</sup> the annual expenditure of \$225,000,000 by the tenth year of the program, to reduce infant and maternal morbidity and mortality.\* Part of this plan already

From the Department of Pediatrics, Duke University School of Medicine, and Duke Hospital.

<sup>\*</sup>Abstract From the Recommendations of the Technical Committee on Medical Care³
"Expansion of the program for maternity care and medical care of children, including health supervision of pregnant women and of infants and preschool children by local physicians, public health nursing services, health supervision of school children, and the services of dentists, nutritionists, health educators and medical social workers. Medical care of mothers and then newborn infants, throughout the period of maternity and the neonatal period, including care of the mothers at delivery in the home or in hospital, and of their newborn infants, by qualified local physicians with the aid of specialized consultants, assisted by nurses, preferably public health nurses, trained in obstetric nursing procedure. Facilities for expert diagnosis and care in diagnostic or consultation centers and in the home. Hospital care as necessary for medical, social, or economic reasons. Health supervision, medical care, and, when necessary, hospitalization of older infants and children—the health supervision and medical care to be provided by quilified local physicians with the aid of specialized consultants in local consultation or diagnostic centers, or elsewhere when the ill child cannot be brought to the center.

"To provide for such an expanding program, an annual cost to federal, state, and

child cannot be brought to the center.

"To provide for such an expanding program, an annual cost to federal, state, and local governments of \$55,000,000 is estimated for maternity care and care of newborn infants, based on the needs of families on relief or with meomes of less than \$1,000 a year (approximately 1,100,000 live births and stillbirths annually), including cost of medical, nursing, and hospital care development and maintenance of 10,000 additional maternal and child health consultation centers to serve smaller cities, towns and rual areas development of centers for postgraduate education of physicians, nurses, medical social workers and federal and state administration. For health supervision and medical care of children, the average unit cost of providing a minimum of essential medical services is estimated to be \$10 per child per year, or an additional annual sum of \$130,000,000 for the 13,000,000 children under 15 years of age in the third of the population in need of financial assistance in obtaining basic health and medical services."

is in effect, i.e., federal and state funds in 1938-39 paid for 50 directors of state bureaus of maternal and child health, 30 of whom have been trained in pediatrics, 28 full-time pediatrists, 13 full-time obstetricians, 2,713 prenatal clinics or conferences, and 6,033 child health conferences, in addition to the personnel of the U.S. Children's Bureau.4 The scope and content of the present program are described below."

Although everyone realizes that additional infant and maternal health services should and must be made available to the public, especially those in the lowest economic group, it must not be forgotten that poverty is not the sole reason for failure to obtain adequate medical service. The fact that the lowest economic group of the public receives less medical care and has more illness3 often may be due to ignorance of the necessity for adequate medical care and of the availability of the present medical facilities. For example, the fact that 19 per cent of the pediatric deaths in 1937 in one state occurred in children who were not taken to their physicians is not prima facie evidence that this absence of medical care was due to poverty and the lack of medical resources. Inadequate pediatric care in many instances is due to the ignorance of the public in availing themselves of the facilities already available, rather than to the lack of medical or economic resources. As illustrations, among the ten diphtheritic patients treated at Duke Hospital during the past month,

<sup>\*&</sup>quot;From the plans submitted by the several states, it becomes apparent that the functions of the state divisions of maternal and child health are as follows (1) To seek the cooperation of the physicians of the state in extending statewide facilities for continuous health supervision throughout pregnancy, infancy, and childhood, and in providing care for sick children and for women at delivery. (2) to seek the cooperation of physicians and all other citizens of the state in informing the public as to what is good maternity care, infant care, and care of children at different stages of growth and development, and how facilities for such care may be made available in each locality of the state, (3) to develop maternity and child health services in all parts of the state through local health units, (4) to aid in the organization of local health units through the provision of child health or maternity services in areas not set fully organized, (5) to be responsible for the establishing of high standards of service in the maternal and child health field (6) to cooperate with all other bureaus of the state health agency in activities affecting the health and welfare of children and mothers, such as public health nursing, control of communicable diseases, including tuberculosis and significant in the state agencies concerned with problems of child health or welfare, as the bureaus of child welfare, departments of education and the agriculture extension service of the departments of education and the agriculture extension service of the departments of education fields of nutrition and dental care, and (9) to promote health ed

"The sustematical child be afth services that the content out under clote allows and the general public."

graduate education in maternity care and care of childr nutrition and dental care, and (9) to promote health ed schools and the general public

"The maternal and child health services that are carried out under state plans are busically those commonly described as health supervision (1) Prenatal clinics and child health conferences conducted by physicians with the aid of public health nurses; (2) home visiting by public health nurses for terching maternal, infant, and child hygiene, and for instruction in bedside nursing care, and (3) nurses' classes of conferences with mothers for educational or follow-up purposes.

"No specific definition of 'crippled child' was given in the wording of the Social Security Act, although secured definitions had been proposed in the hearings before Congress. An investigation of the laws under which state agencies were operating showed variations extending from a very strict definition and interpretation, which include all physically handicipped children who could be benefited by medical or surgical treatment. The valous definitions of a crippled child incorporated in the actual practice definitions will be broadened gradually to include as wide a range of A few states have been accepted for the present, with the lidea that in crippling conditions is present within the limitations of the available funds, but most of the cases accepted for care have been orthopedic and plastic conditions. See the past do of children as within the proportionately more care may be given discuss the case is common. Children whose chief disability is incurable blindness, de efficies, are considered by and the scope of this program's a considered by and conditions considered by and those having thours little sequiring permanent custodial care considered by and the scope of this program's

eight were not taken to their physicians for an average of five days after the onset, and, of nine other children suffering from diphtheritic paralvsis, seven were not taken to physicians until the onset of paralysis.5 The parents had not realized the possibility that a "sore throat" might be diphtheria. Yet diphtheria antitoxin is supplied at cost by the state laboratory and is given free in many counties. Although free toxoid is supplied and its usage is urged by health departments, many parents fail to appreciate its value." In Durham County, which is typical of most American counties, the medical profession, the infant feeding clinics, the health department, the county physician, and the Watts, Lincoln, and Duke Hospital Clinics can provide the necessary preventive and therapeutic measures, regardless of the poverty of the patient, if the public is made aware of their necessity. The Durham-Orange County Medical Society recently has authorized a series of unsigned newspaper articles on preventive pediatrics, calling attention to the unnecessary deaths, and the means of preventing them. Syndicated medical articles have made remarkable progress in educating the public. but as yet they do not reach those who do not read the newspapers.

National, state, county and city advertising campaigns in newspapers, buses, billboards, and radio, and through churches, schools, the Parent-Teachers' Association, the American Legion, etc., on the necessity for antenatal, natal and postnatal care and the medical facilities available. conducted by publicity experts, are necessary to reach more of the population. If, through advertising, a public demand can be created for automobiles, electric iceboxes, certain brands of cigarettes, and patent and home medicines (which represent 14 per cent of the present medical costs<sup>6</sup>), cannot the people be taught to seek adequate medical service? Better pediatric and obstetric care and a lower infant and maternal mortality can be obtained by a smaller amount of money spent in teaching the public to utilize the present medical facilities than would be required for providing additional medical resources. After an educational program has produced a demand for more medical care, the medical services can be extended as they are needed. The public gets the product it demands, whether it is medical care or a nationally advertised variety of tooth paste. The American Academy of Pediatrics shortly will start such a pediatric publicity campaign.

Increased education of the public, in addition to increasing the amount of medical service requested, will raise the standard of that service. If a public demand for preventive pediatrics is created, physicians who are not familiar with modern methods will seek postgraduate training to help their patients.

This need for the education of the public is indicated by a recent study of chronically diseased adults who were not receiving medical care;

<sup>\*</sup>Immunization against diphtheria was made compulsory in North Carolina in March, 1939.

80 per cent of them failed to obtain this care through ignorance and the need of education and only 10 per cent because of economic reasons. That public education can be efficacious and that the money for cancer publicity was well spent are demonstrated by the fact that among cancer patients, only 37.4 per cent went without medical care through ignorance and 1.5 per cent for economic reasons. A similar public education campaign for preventive pediatrics should be equally fruitful.

If this program or some modification of it is adopted and is intelligently operated by pediatrically trained physicians, many of the preventive measures recommended will be made effective among the underprivileged one-third of the population for whom the plan was recommended. In addition, the children of the remaining privileged two-thirds of the people also will receive greater preventive care, as a result either of the stimulus or of the extension of the government-aided program.

Although many more children than formerly are getting adequate pediatric care and although there is a much greater number of qualified physicians among whom the patients are divided, this greatly needed increase in preventive pediatrics will necessarily modify the practice of the specialty. The bulk of the care of children and the carrying out of the preventive measures will be and should be in the hands of general practitioners, mow that the teaching of pediatrics has been improved, and the feeding of infants has been simplified. Many of the present pediatrists probably will become salaried members of state and federal health organizations and will be responsible for the supervision and consultation necessary to effectuate the program for the reduction of infant and maternal mortality. This new status of pediatrics will be similar to the changes wrought in private school teaching by the universal public education movement at the turn of the century.

Recent medical graduates who are primarily interested in pediatrics will still have the same four choices of careers, though the proportions will change, i.e., the majority probably now will prepare themselves for general practice instead of going into pediatrics as a specialty, and the minority will become private pediatrists, government consultants, and teachers of pediatries.

The private practice of pediatries, though limited by the federal and state child health programs and the better training of general practitioners and medical students, will still remain because children have needs which are different from those of adults. However, the numbers of ill children probably will be reduced through preventive measures.<sup>8</sup> To remain successfully in private practice, the pediatrist must continue to lead in preventive measures and also include mental hygiene and adolescent problems in his field.<sup>10</sup>

The greatest present pediatric need is in rural communities, and it can only be met by encouraging younger well-trained general practi-

<sup>\*</sup>See footnote p. 810, "Abstract From the Recommendations, etc."

tioners to forsake the medically overcrowded cities. Unfortunately, the city youth often is ill-fitted for country life and practice: it is necessary to provide means, probably through loan funds, for the rural student to study medicine. 11 Analyses indicate that the majority of them return to the country. 12 The law of supply and demand is causing a larger percentage of the present graduates to enter general practice, but the number going into rural practice is still falling. 13 except in North and South Carolina. In these two states the establishment of rural hospitals through the aid of the Duke Endowment is improving medical service in the country and attracting young physicians there. In addition, such local hospitals influence older physicians, who have kept abreast of the times, to remain in rural communities.14 The subsidizing of hospitals and the building of new ones as they are needed, advocated by the Technical Committee on Medical Care,3 will have a similar result.

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# Critical Review

## TUBERCULOSIS IN CHILDREN

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A STHERE justification for assuming that the problems in tuberculosis have been solved, that the answers to pathogenesis, resistance, immunity, allergy, and many others have been found, and that complete and permanent control of the disease in the human being can be accepted as being definitely assured? How many of the newer ideas and concepts which have been brought forth in recent years are established facts, and how many of them are but ingenious theories to explain unknown processes which will have to be modified as time reveals the true situation? Certainly the literature of the past year leads one to the inescapable conclusion that instead of unanimity of thought, the newer knowledge has only stimulated controversy, created new and unexpected problems, and resulted in expressions of uncertainty and widely divergent opinions. Unquestionably this state of affairs is highly desirable if true progress is to be made, but it is somewhat disconcerting.

For the most part, the conflicting views have to do with various aspects of primary tuberculosis, and particularly with the relation primary infections bear to the development of reinfection tuberculosis. In previous reviews we have attempted to set forth the essentials of the many concepts as they have been published. These need not be repeated here, except for purposes of clarification. Our aim in this review is to continue to present such recent studies and contributions as seem to us to make a point on one side or the other in elucidating some of the more important present-day issues. The first part of the review will deal almost exclusively with primary tuberculosis. We shall also summarize the work which has been done in tuberculin studies.

However, before taking up the review proper, we should like to call attention to two important publications which have been published recently. The first of these is the second edition of Tuberculosis Among Children and Young Adults, by J. Arthur Myers. This volume represents a summary of the conclusions which the author and his associates have reached from their many years of longitudinal study for tuberculosis of thousands of children and young adults carried on at Lymanhurst and elsewhere in the University of Minnesota. The contributions which this distinguished group of physicians have made to the better understanding of the evolutionary course of the tubercle have received world-wide recognition, and, while agreement with some of their views has not been universal, nevertheless, the influence of their work in molding thought has been recognized everywhere. Since much of the material in Dr. Myers' book has been previously published in various medical journals concurrently with the progress of his studies and since the essential concepts in these articles have been previously reviewed in these pages, we shall refrain from commenting further upon the subject matter in this new volume, profitable though that might be. We may add only that the volume affords the practitioner and the student alike a ready source for gaining up-to-date knowledge of the newer concepts in the whole field of tuberculosis, from infancy to old age, and the extensive bibliography appended to each chapter offers a guide to any desired supplemental reading.

The second publication referred to is the eleventh edition of Diagnostic Standards<sup>2</sup> published by the National Tuberculosis Association. Instead of being called the eleventh edition, however, this work is designated nated as the "Tentative Edition-1938." A word of explanation as to the reason for this title is interesting and lends support to the thought expressed in our opening paragraph. The brochure was prepared by a committee of ten expert phthisiologists appointed by the president of the National Tuberculosis Association in 1936. Their original manuscript was submitted to numerous clinicians and further modified according to replies received, but still left certain points in doubt or disagreement. Offered tentatively in its present form, the committee hopes to elicit further comments from specialists, general practitioners, and public health administrators, which "will lead to the formulation of standards and definitions which will be more universally acceptable." Because of the source, the statements made in this booklet are generally accorded an "official" status. Officially then the terms "childhood type" and "adult type" tuberculosis have been dropped, to be replaced by the more satisfactory terms "primary tuberculosis" and "reinfection tuberculosis" respectively. This change is in keeping with clinical experience, in that primary tuberculosis may occur at any age period and reinfection tuberculosis is seen in childhood as well as in adult life. Furthermore, the new terminology coincides with international usage. should find Diagnostic Standards a very useful pamphlet. In condensed form it gives the essential features of both primary and reinfection tuberculosis and the pathogenetic correlations of all forms of tubercu-It defines terms, describes technical procedures, and presents a classification and descriptive summary form so framed that it may be adapted readily to any kind or location of tuberculous lesion. These forms may be purchased in quantities from the National Tuberculosis Association or its affiliated associations.

### PRIMARY TUBERCULOSIS

Definition.—As has been indicated, much confusion exists in the literature in respect to many phases of the primary infection. In the matter of definition, for instance, there are two rather distinct schools of thought. One group (rather extensive in this country) accepts the viewpoint developed at Lymanhurst by Stewart, Harrington, and Myers.<sup>3</sup> In essence, this concept considers first or primary infections to be those resulting from implantation of virulent tubercle bacilli upon nonallergic soil. When such infections occur in the lungs, the resulting lesions are, first, a primary pulmonary focus (or multiple foci); second, tuberculosis of the associated hilus glands; and third, foci in distant organs as the result of preallergic hematogenous dissemination of bacilli. In a few of the cases, coincidentally with the development of allergy, which takes place in from three to seven weeks after the initial infection, there occurs a collateral inflammatory reaction about the primary pulmonary focus of sufficient size and density to be demonstrable roentgenologically. The invariable course of the lesions of first infection tuberculosis, where

no new postallergic exogenous or endogenous reinfection occurs, is one of slow retrogression, encapsulation, calcification, and in some instances, ossification or complete disappearance of the lesions. First infection tuberculosis is, therefore, considered to be a routine benign disease, regardless of the age at which it occurs. A postallergic extension, or appearance of new tuberculous pathology beyond the limits occupied by the original set of primary lesions, marks the onset of a reinfection type of the disease. Thus, tuberculous meningitis, miliary tuberculosis, and tuberculous bronchopneumonia are regarded as acute manifestations of reinfection tuberculosis, whereas phthisis is a chronic form. Hence, this concept takes into account the part played by allergy in the production of all the serious and fatal forms of tuberculosis.

The opposing group draws no such line between the primary infection and the acute reinfection forms. Diagnostic Standards states, "By 'primary tuberculosis' is meant the totality of the morbid processes following directly and uninterruptedly the first implantation of tubercle bacilli. It is obvious that in many instances no sharp line of demarcation can be drawn between primary and reinfection tuberculosis. that the appearance of allergy marks the end of primary tuberculosis (as is frequently suggested) would mean that no clinically recognizable and diagnosable phase of tuberculosis could be so designated." While the most frequent development of the primary complex is one of slow retrogression, in a minority of cases, the percentage of which is hard to estimate, and particularly in infants and in children exposed to prolonged infection, and more frequently in colored than in white children. the primary complex does not heal promptly but becomes progressive. Progress may occur at the site of the primary pulmonary focus leading sometimes to a large excavating pneumonia, or the progressive primary focus may rupture into a bronchus with resulting bronchogenic spread. Similarly primary lymph node lesions may progress to rupture into a bronchus, or bacilli may finally reach the circulation through efferent lymph channels to proximal lymph nodes. Transported by the blood, the bacilli may cause single or multiple lesions in the lungs, meninges. bones, kidneys, and other organs. Thus miliary tuberculosis, tuberculous meningitis, and tuberculous brochopneumonia in this concept are considered as being part of the primary infection. Viewed in this light. first infection tuberculosis is by no means a benign disease. In a further analysis of the differences in opinion, two significant points need to be stressed. In the Lymanhurst concept the fundamental difference between primary and reinfection tuberculosis is allergy. In the viewpoint as defined in Diagnostic Standards, the difference between the two is in the manner of progression of the lesions. The differences are clearly brought out by quoting a statement from Pinner,4 who says: "In the progression of tuberculous lesions is found, probably, the clearest expression of the differences between primary and secondary infections. The functional difference between the two is allergy. Pathogenically the differences are that in the progression of a primary lesion all available routes of propagation of bacilli come into play: lymphatics, blood stream, preformed channels. In secondary infection, dissemination through the lymph and blood stream is quite infrequent, increasingly so with the increase of time clapsed between primary and secondary infection. Progression by continuity and through preformed channels is common in secondary infection. Thus as a characteristic example of progressive disease following more or less closely upon primary infection

is seen generalized miliary tuberculosis, frequent in childhood, rare in later life. The characteristic progressive disease of adult life is tuberculosis limited to one organ system, such as pulmonary phthisis, rare in

childhood, frequent afterward."

The definition of primary tuberculosis, as contained in *Diagnostic Standards*, to the effect that the appearance of allergy marks the end of the primary infection, seems susceptible to challenge. We are aware of no such viewpoint. If, as we suspect, the reference is to the Lymanhurst view, it is a misconception of this idea. The appearance of allergy marks the end of the period when new exogenous or endogenous infections react as do primary infections, but the original first infection which produced the allergy, unless interrupted by death, will retain the characteristic features of the primary complex through all the stages of resolution and calcification, regardless of superimposed secondary infections. In other words, primary complex and primary infection are essentially synonymous terms in this concept.

Carroll<sup>5</sup> from the Undercliff Sanatorium for Children in Connecticut, after observing some 3,300 children over a period of seventeen years, states that he has reached much the same conclusions regarding tuberculogenesis as have Myers, Stewart, and their associates at Lymanhurst. He believes it to be "a fundamental principle that tuberculous lesions arising in allergic and in nonallergic tissues have vastly different clinical expressions." Pathologists, on the other hand, seem more inclined to the view that, while it is usual, it is not an invariable rule, for the lesions of the primary complex to progress to anatomic healing. Auerbach,6 pathologist at the Sea View Hospital in New York, reports seventeen cases autopsied in a period of four years, in which progression occurred in the primary complex. With one exception the children were negroes: fifteen of them were between the ages of 1 and 3 years. The author describes the various degrees of caseation, liquefaction, and cavitation encountered, and explains the pathologic features which serve to differentiate primary from tertiary excavations. Macgregor and Alexander of Edinburgh, on the basis of some two hundred pathologic examinations of eases of primary thoracic tuberculosis, describe the various modes of origin of localized extension and widespread dissemination from the primary lung complex. That the point of view is not one to be easily settled, even by workers of such extensive experience, is shown by the following quotation from this article, "When there is severe and widespread pulmonary tuberculosis, the question arises of what part, if any, is played by repeated exogenous reinfection in the pathogenesis of the disease. Does the whole trouble arise from the progressive spread of infection from a single primary focus, or are new infections from without responsible for at least a part of the widespread dissemination? The question is difficult to answer with any certainty. On the one hand, it is often possible to trace, with at least a fair degree of plausibility, the progressive evolution of the pulmonary lesions from their origin in the primary focus. On the other hand, many children who develop this grave type of pulmonary tuberculosis have been exposed to the risk, or indeed the certainty, of repeated heavy infections, perhaps from a tuberculous mother or other member of the household.

Perhaps sufficient has been said to establish the point that confusion exists regarding the delimitations of primary infections. The problem would seem to be of some importance, for to one group the primary infection is a benign form of tuberculosis seldom resulting in disease

or death, while to another group it is a serious disease accounting for practically all the deaths from tuberculosis in early childhood. Perhaps it is more a matter of definition than anything else, but even so it would be advantageous if everyone "talked the same language."

Endogenous Reinfectivity.—Another controversial subject has received renewed impetus as the result of the report by Feldman and Baggenstoss' upon the residual infectivity of the primary complex. Heretofore, wide acceptance has been given the opinion that tubercle bacilli may remain viable in the centers of the calcified pulmonary and lymph node foci of first infection tuberculosis for many years, and possibly throughout the lifetime of the individual. The persistence of a positive reaction to the tuberculin test in otherwise healthy persons is most frequently explained on the basis of continual production of tuberculoprotein from bacillary activity within the lesions of the primary complex. Those who contend that the pathogenesis of reinfection tuberculosis may have an endogenous source assume the latency of the lesions of the primary complex or of the secondary hematogenous foci established in the preallergic postinfectious period. Thus Myers¹ from his long experience at Lymanhurst has frequently referred to the primary complex as being a double liability, in that it first creates tuberculo-allergy, and then for years after harbors a potential source of living organisms which may at any time become liberated to set up a focus or foci of reinfection tuberculosis. In support of this view he has pointed to the work of Robertson, of the Mayo Clinic, who concluded after an extensive study of autopsy material that apparently healed tuberculous lesions may become clinically active after varying intervals. Wallgren, 10 whose opinion is probably representative of continental Europe, even goes so far as to maintain that pulmonary tuberculosis is always of endogenous origin, although not necessarily from the primary complex. He believes that in tuberculosis, as in syphilis, a primary infection establishes an immunity which is effective against all ordinary exogenous reinfections. but not against extensions of the disease already present within the body. In his judgment, most often pulmonary tuberculosis arises from secondary hematogenous foci in the lung (escapes from the primary complex) in those individuals who possess a special disposition to tuberculosis, and who have reached the age of puberty. Thus many competent observers are convinced of the truth of the statement, "once tuberenlous always tuberculous."

Now, however, Feldman and Baggenstoss, also of the Mayo Clinic, have most carefully examined a total of 103 specimens obtained from 68 unembalmed bodies of human beings who died from causes other than tuberculosis and have found viable tubercle bacilli in only one instance! Forty-one of the specimens were from Ghon tubercles, fiftyfive from hilar lymph nodes, five from apical scars, one from a mesenteric lymph node, and one from a tuberculous thymus gland. The ages of the individuals varied from 7 to 90 years, the greatest number being in the fourth, fifth, and sixth decades. Eight tubes of culture material and two guinea pigs were inoculated with emulsified material obtained from each lesion. The authors believe the methods employed in the study were such that if live organisms had been present they would have been found. The one positive result was obtained from an encapsulated caseocaleareous Ghon tubercle in the right lung of a man 54 years of age. A Ghon tubercle in the left lung gave negative results. Feldman and Baggenstoss conclude that "in adults, endogenous reinfection is unlikely to occur from lesions of the primary complex." It is doubtful if this important and excellent study will be generally accepted as having offered convincing proof of the conclusions reached. As stated in a recent editorial, it does prove beyond question that the lesions of the primary complex may and do heal completely, and to this extent refutes the assertion "once tuberculous, always tuberculous." However, on the basis of the limited scope of the authors' investigation, further conclusions are probably not justified. All the individuals studied were admittedly free from gross tuberculous disease. Would an equally careful search for organisms in a group of individuals with active pulmonary disease give the same negative results? May it not be that the reason for the absence of active tuberculous disease in the bodies examined was that the lesions of the primary complex had become sterile? Furthermore, the report does not consider the possibility of endogenous reinfection as maintained by Wallgren. Without question this work by Feldman and Baggenstoss will stimulate many other investigators to study the problem from all angles, with the desirable prospect that the near future will bring clarification to the present muddled situation of exogenous versus endogenous reinfection.

Healed Primary Complex .- Before leaving the subject of healing in the lesions of the primary complex, there is another closely related phase of the problem which merits attention. This has to do with loss of hypersensitivity in individuals previously known to have reacted positively to the tuberculin test, and with unmistakable x-ray evidence of tuberculous lesions in individuals who react negatively to maximum doses of tuberculin. It is usually stated that healthy individuals previously infected with tuberculosis will react positively to the tuberculin test if 1 mg. of old tuberculin or the second dose of purified protein derivative is used. A negative test with these doses is generally accepted as excluding tuberculosis. From recent data obtained in retesting surveys, evidence is accumulating that this may not be entirely true. For instance, Tortone, Chattas, Myers, Stewart, and Streukens,<sup>12</sup> in a study of tuberculosis in Lymanhurst children under six years of age, report that during the course of a follow-up study twenty-two children who previously were sensitive to tuberculin later lost their sensitivity and gave negative reactions to repeated intracutaneous injections of 1 mg. doses of old tuberculin.

Rich<sup>13</sup> cites the reports of Lloyd and MacPherson from England, who found that of 303 healthy London children who reacted to 1 mg. of old tuberculin in 1930, 2 per cent were negative to that dose two years later; of Aronson who followed 87 tuberculin-positive urban children for a period of five years, during which time 9 per cent became negative to 1 mg. of old tuberculin; of Horan who tested 197 adolescent boys yearly for three successive years and found that 14 per cent of those positive on the first test lost their sensitivity; and of Paretzky who reported that of a group of tuberculin positive children followed up to five years, 80 became negative to 1 mg. of old tuberculin, and 64 per cent of these failed to react to 10 mg. of old tuberculin. Rich also cites the following reports of tuberculous lesions demonstrable by x-ray in persons who reacted negatively to tuberculin. Barnard, Amberson, and Loew found that of 184 school children between 12 and 15 years of age who had tuberculous lesions demonstrable by x-ray, 6 per cent failed to react to 1 mg. of old tuberculin. Wells and Smith found

demonstrable x-ray lesions in 5.5 per cent of 128 individuals who presented negative reactions to 1 mg. of old tuberculin. Opie and his associates showed that 15 per cent of 186 children between the ages of 5 and 19 years who were negative to 1 mg. of old tuberculin had definite x-ray evidence of tuberculosis. Crabtree, Hickerson, and Hickerson found 17 per cent of a group of persons over four years of age who were negative to 1 mg. of old tuberculin to have calcified lesions on x-ray examination.

The implications of these findings raise many interesting speculations. If one believes the persistence of tuberculin sensitivity to be due to viable tubercle bacilli in the primary complex, then these clinical observations lend direct support to the results obtained by Feldman and Baggenstoss at autopsy: that a certain number of primary complexes will undergo complete healing. However, if one believes that persisting sensitivity results from repeated small exogenous reinfections, one must consider whether the marked decline in morbidity and mortality rates from tuberculosis may not be playing an important part in its loss by greatly reducing the opportunities for chance contact with tubercle bacilli. At any rate, it appears certain that a proportion of the population who have experienced primary tuberculous infections, but who are no longer allergic as measured by the tuberculin test, will reach adult life. What form will subsequent tuberculous infections take in these individuals? Will they follow the characteristics usually associated with primary infections; namely, a pulmonary focus located anywhere in the lung, marked involvement of associated lymph nodes, and a strong tendency to retrogression by encapsulation, calcification, and ossification; or will they follow the reinfection type of disease characterized by apical or subapical parenchymal lesion, little or no involvement of associated lymph nodes, prominent fibrosis, and a tendency to caseation, liquefaction, excavation, and bronchogenic spread? The longitudinal observation of the fate relative to tuberculosis of such persons offers an opportunity to shed light upon the obscure relation now existing between allergy and immunity or resistance. If allergy and immunity are identical, it would seem logical to suppose that they would again undergo a primary infection if sufficiently exposed to produce disease. On the other hand, if the disease process followed the pattern of reinfection tuberculosis, it would be strong evidence of resistance remaining even though allergy had been lost. To the best of our knowledge, no reports have appeared in the literature of observations made under these exact conditions.

Primary Infections in Adults.—Reports are appearing concerning the clinical and pathologic aspects of the type of tuberculosis developing in young adults who have not previously experienced known primary infections. Here again we run into decidedly conflicting viewpoints. It is interesting to compare what such unquestioned authorities as Rich, Myers and co-workers, Mand Sweany have to say on the subject. All agree that a changed situation in the civilized world has taken place in recent years. Formerly it was probably true that the majority of persons had received primary infections by the time they reached young adult life; today, tuberculin surveys indicate that the rate of infection has fallen to such a degree that from one-half to three-fourths or more of young people are reaching high school and college age without having been infected. Rich maintains that if more than half of the present crop of young adults have grown up uninfected, we should be encoun-

tering on all sides many instances of primary tuberculosis demonstrable both clinically and pathologically, but that such is not the case. "Young adult tuberculosis, both at the bedside and at the autopsy table, has today precisely the same characteristics as that during the period when primary infection in urban adults was almost universal." He points out that in other countries (Sweden and Germany), apparently true cases of primary tuberculosis in adults have been observed. He concludes "that either our long held concept of the pathogenesis of adult type tuberculosis requires a drastic revision, or else that many individuals who today are tuberculin negative have really been infected, and have retained their acquired resistance to the degree that determines the peculiarities of adult type tuberculosis, but have lost their hypersensitivity and under present conditions of diminished opportunity for reinfection they remain tuberculin negative for longer periods than would have been the case formerly."

Myers and his co-workers,14 on the contrary, are convinced from their observations on students of medicine and nursing that primary tuberculosis does occur in young adults and that it runs the same course and has the same characteristics as the disease in infants and children. They cite one school of nursing with a tuberculosis service in which approximately 22 per cent of the students entering as probationers reacted positively to the tuberculin test, but on graduation 94 per cent gave positive reactions. Under such conditions they have had an opportunity to observe shifts from negative to positive reactions within relatively short periods of time. Furthermore, x-ray studies made on such positive reactors have usually been negative. In the occasional instances in which the x-ray film has revealed the site of the primary focus in the lung, the lesions have been observed to persist for many months, with no signs of illness, and eventually to resolve or disappear altogether. Commenting further, the authors say, "Some have suspected these shadows to be caused by reinfection type of lesions because some of them are located in the subclavicular region. Such interpretations are based on the assumption that all young adults have been previously infected and later lost their allergy. We have not been able to obtain any evidence to substantiate such an assumption. Since only approximately 1 per cent of the population becomes infected each year in the community investigated, this fact does not permit us to assume that 100 per cent of the young adults we have observed have been previously infected. To us, the location of the lesion is no criterion as to its type, since we have repeatedly seen the first infection type of tuberculosis in children appear in the apex or subclavicular region, as well as the basal parts of the lungs." In addition, the authors state they have seen reinfection tuberculosis appear in a number of the young adults who developed primary complexes while under observation, months or years after the first infection type of disease was discovered.

Sweany, 15 pathologist at the Chicago Municipal Tuberculosis Sanitarium, presents a view midway between that of Rich and the Lymanhurst group. He finds that because of the reduced infection rate many more people are receiving their primary infection in adult life but that these primary infections are not recognized as such because they are frequently atypical. One of these atypical features is that the primary lesion tends to become more localized in the parenchyma of the lung, but overflows into the surrounding tissues by a direct chain of colonies to set up an area of reinfection tuberculosis, and this within a

much shorter space of time than usual. Only by careful study can the primary infection be distinguished from the reinfection type. A second atypical feature is the lymph node involvement, the extent of which is not nearly so great in cases of adult primary tuberculosis as in childhood tuberculosis. Sometimes the nodes of the hilum are not even reached. Herein, perhaps, lies the explanation for the infrequency of hematogenous spread (meningitis) of the tubercle bacilli in adults as compared with infants and children. Sweany conjectures that the lessened involvement of lymph nodes may be due to changes in the lymphatic anatomy as the individual advances in age or that some nonspecific factor acquired from other infections may localize the germs and prevent their free spread by the lymphatic system. His conception is then that the pattern of primary tuberculosis follows the typical course in infants, children and primitive adults, but that in civilized adults, it tends to take on many of the features of reinfection tuberculosis, but is distinguishable from the latter.

Mortality.—There is yet another phase of primary tuberculous infection about which agreement is conspicuously lacking. This has to do with the mortality rate suffered by infants and children who become infected with the tubercle bacillus for the first time. However, this applies only to the age period under 5 years, and more particularly to the period of infancy, from birth to 2 years of age. There is no disagreement that the "safest" period in the entire life cycle as far as risk to life from tuberculosis is concerned, is from 5 years to puberty. Rich<sup>13</sup> states that "by far the most dangerous age period in which to be infected, from the standpoint of the chance of succumbing during that age period, is that of the first five years of life, and most particularly during the first year." Myers, on the other hand, declares that after fifteen years of observation he finds "a very small percentage of the infants who had first infection type of tuberculosis died of that disease in infancy or early childhood." Several studies bearing on the topic are available for reference.

Dorothy Price,16 of Dublin, reports on the outcome in 78 cases of infants suffering from tuberculosis. Of these patients, 60 or 77 per cent have died, and 18 or 23 per cent recovered. Twenty-two of the deaths resulted from caseous pneumonia spreading from broken down primary foci; 18 from miliary tuberculosis; and 17 from tuberculous meningitis. In addition, there were two deaths from abdominal tuberculosis and one from congenital tuberculosis. Of the 18 patients who recovered, all had a history of family contact, all had positive tuberculin tests, and all had positive pulmonary x-ray findings. Eight of the infants were under 6 months of age when first observed. This study contributes little in supplying an answer to the question of how infants tolerate tuberculous infections, for it merely represents a collection of the majority of the infants in Dublin who developed manifest signs of illness. One would like to know how many other infants in Dublin in the same age period were infected, but did not come under observation, presumably because no signs of illness developed. The report of the 18 children who recovered, although parenchymal disease was demonstrable, furnishes indisputable proof that tuberculous disease in infancy is not necessarily fatal, as was at one time held to be the almost universal

Braily's observations<sup>17</sup> on the course of tuberculous infections in infants and children carried on for a period of eight years at the Harriet

Lane Tuberculous Clinic in the out-patient department of Johns Hopkins Hospital, supply a most reliable and significant source of information regarding the problem under discussion. A total of 223 children, of whom 91 were white and 132 colored, are included in the study. All of them were found to be tuberculin positive before 2 years of age. Only 9, or 10 per cent, of the 91 white children have died in the eight years of observation. Eight of the deaths occurred within the first year from discovery of the infection, and one additional death occurred in the first five-year period. Thirty-two of the white children showed a parenchymal lesion on the first x-ray examination, and eight of the deaths occurred in this group. Only one death from tuberculosis occurred among the 59 white children whose first x-ray examination showed no parenchymal lesion. One additional fact of importance is that infants known to be infected before 6 months of age had a mortality rate nearly twice as great as children found to be infected between 6 months and 2 years of age. The colored children in Braily's series did not fare as well as the white children. Not only was the mortality rate among them more than three times as high, but they also showed a greater tendency to develop parenchymal lesions, a fact which undoubtedly explains the increased risk to life.

A study equal in value and merit with that of Braily's is one by Tortone, Chattas, Myers, Stewart, and Streukens<sup>12</sup> on the fate of 629 Lymanhurst children under six years of age, known to be infected with tuberculosis and followed over an average period of five years. Ten, or 1.6 per cent, died from tuberculosis. Pneumonic infiltrations characteristic of the acute stage of primary pulmonary tuberculosis were demonstrable roentgenologically in 155 of the children; 268 had normal chest films; and the remainder showed calcification, either as Ghon tubercles or in the hilus lymph nodes, or both. Nine of the ten deaths occurred among the group with pneumonic infiltrations which did not form Ghon tubercles. One child in the age period from 1 to 2 years with calcified hilus glands died, presumably of tuberculosis. Five or 9.6 per cent of the 52 children in the group under 1 year of age died, and five or 3.8 per cent of the 132 children in the age group from 1 to 2 years of age died. No deaths occurred in later age periods.

If only the white children are considered, the experiences at the Harriet Lane Clinic and at Lymanhurst have been strikingly similar. The studies justify the drawing of fairly definite conclusions relative to infants and young children infected with tuberculosis.

- 1. At least 90 per cent of white children infected with tuberculosis within the first five years of life may be expected to survive their tuberculous infection.
- 2. Such mortality as there is will be almost entirely confined to the first two years of life.
- 3. The risk to life is over twice as great in infants who become infected in the first year of life as in infants who do not become infected until the second year.
- 4. The great majority of all tuberculous deaths will occur among the group of infected infants whose chest roentgenograms reveal a parenchymal lesion.

If further proof is desired of the ability of infants to resist severe tuberculous infection, one needs only to recall the unfortunate occurrence at Lubeck in 1930, when by error 251 newborn infants were given virulent tubercle bacilli, instead of the supposedly avirulent Bacillus Calmette Guérin culture. Seventy-two of the infants died of extensive tuberculosis in the first year, but the remainder, or 71 per cent, resisted the infection.

Immunity.-A final point of particular interest is the question of the immunizing effect (or lack of it) of primary infections. Here again diametrically opposed opinions are freely expressed. One school holds that primary infections, successfully withstood, impart an immunity which is effective in preventing all subsequent ordinary reinfections. As proof of their contention, they point out that while 50 to 60 per cent of the adult population are infected, only about 1 per cent ever develop clinical disease. The opposing group believes that primary infections not only fail to immunize but that on the contrary they furnish the essential prerequisites which lead to the development of reinfection tuberculosis, namely, allergy and a potential source of tubercle bacilli. Ch'iu, Myers, and Stewart<sup>18</sup> submit a study in support of the latter viewpoint. During the eight-year period from 1921 to 1928, 446 positive and 772 negative tuberculin-reacting children came under observa tion at the Lymanhurst Health Center. The positively reacting children were followed for an average of 11.3 years, and the negative reactors for an average of 10.95 years. The average age of the former when first seen was 7, and of the latter 6.6 years. At the end of the observa-tion period it was found that 67, or 15.02 per cent, of the 446 positive tuberculin reactors had become ill with reinfection type of disease, while only 13 or 1.68 per cent of the 772 negative reactors had developed clinical disease. There were 22 deaths among the former group and only 1 in the latter, giving a mortality ratio of positive and negative reactors of 38 to 1. Thus the study shows that tuberculous disease developed nine times more frequently among the positive reactors than among the negative ones. Commenting on their findings, the authors state, "With 15 per cent of the children who reacted positively to the tuberculin test, with no other findings of clinical disease, falling ill within approximately the next ten years, it is obvious that a tuberculin reaction in a child is of far more significance than we formerly believed. If the morbidity and mortality continue among the individuals throughout the span of life as they have begun, clinical tuberculosis will be as frequent among them as is tertiary syphilis among previously positive Wassermann reactors. This would seem to be sufficient evidence to dispel any great enthusiasm for immunity produced by the primary tuberculous complex. Indeed, by our old criterion this is the group that should have been immunized by reason of infections in childhood. One might maintain that the remaining 85 per cent have been immunized. but any argument in this direction at present would be nothing more than speculation; only time will tell, and, since no observations have previously been made, it would be futile to venture an opinion. Suffice it to say that 15 per cent is a large toll to be exacted in so short a time."

## TUBERCULIN STUDIES

The importance which tuberculin testing has come to assume in the campaign for the control of tuberculosis has led to the undertaking of many valuable studies, both laboratory and clinical, concerning tuberculin and its use. Some of the more significant of these studies are summarized in the following paragraphs.

One of the most startling contributions is that of Gruskin, Louria, Bennett, and Schwartz<sup>19</sup> of Temple University, who introduced an intradermal test for the determination of activity of tuberculosis. test is based on the reaction to homologous proteins comparable to the intradermal tests for malignancy and pregnancy. The mechanism of the reaction consists in the intradermal injection of antibody (homologous protein), and depends upon the antigen formed within the organism during the active phase of the disease responding by the formation of pseudopodia. An extract of fibrin, obtained from guinea pigs which have been previously injected with a suspension of tubercle bacilli. is the material employed in performing the test. The test is read within three to five minutes after the injection and is considered positive if pseudopodia appear. The authors report from 92 to 96 per cent positive skin tests in some five hundred cases of active pulmonary tuberculosis proved by x-ray, sputum examination, or guinea pig inoculation. Positive tests were also found in a small series of cases of extrapulmonary tuberculosis. Negative tests were recorded in a few pathologic states which were not tuberculous. Obviously, a test which would differentiate between active and inactive tuberculosis would be a most valuable addition to our diagnostic armamentarium. However, the value of the test advocated by Gruskin and his co-workers must be subjected to a much more severe application before any appraisal of its value can be made. Certainly future experiences with the test will be watched with a great deal of interest.

The possibility that tuberculin used in making tests may in itself induce hypersensitivity so that subsequent tests give rise to false positive reactions has received considerable attention in the past. Seibert<sup>20</sup> has shown that the sensitizing potentialities of the various tuberculoproteins are related to their molecular weights. Thus MA-100 with a molecular weight of 26,000 sensitized nontuberculous animals, whereas purified protein derivative with a molecular weight of 2,000 to 3,000 did not do so. In a very careful and exhaustive study, Nelson, Mitchell and Brown<sup>21</sup> sought an answer to the question, "Is tuberculin, in amounts ordinarily used for skin testing, capable of producing sensitization to itself in man, and if so, do different tuberculins vary in this respect?" 800 children were employed in the study varying in age from young infants to children ten years of age and over. Selection was made on the basis of negative reactions to two preliminary screening tests. material used was MA-100, old tuberculin, and purified protein derivative. In order to cover as many possibilities as desired and to facilitate comparison, the children were divided into four groups. Roentgenograms of the chest were made on approximately one-half of the children. As many as fourteen tests, made with each of the three materials and at varying intervals, were given in some of the groups. A reacting area of 5 mm. or more in diameter was considered positive. A considerable number of the children reacted to the third test which was performed four days after the first test. However, the authors conclude it does not appear probable that sensitization to tuberculin was induced because "first, of the fact that the third injection was performed 96 hours after test one, an interval presumably too short to permit induction of sensitization; second, of the marked individual inconsistencies in the various series of tests; third, of the failure to develop increasing rates of response or to secure increasingly larger reactions in the individual child: fourth, of the roentgenologic evidence of previous tuberculous

infection in children who, although they did not react to the first two tests, did have reactions larger than 5 mm. of edema in one or more of the subsequent tests; and fifth, of the similarity of 24 and 48 hour responses to 0.005 mg. of purified protein derivative of children who had had repeated injections over a period of two years with that of a group in the same institution who had no reactions to a test 48 hours previously with 0.00002 mg. of purified protein derivative, but who had not had repeated injections."

Another practical study regarding the use of tuberculin is contributed by Lincoln, Raia, and Gilbert,22 of Bellevue Hospital. In the first place the authors agree with the conclusion reached by Nelson. Mitchell, and Brown, that sensitization to tuberculin from repeated injections is not likely to occur. They gave from four to seven injections of old tuberculin in the same site at two- to five-day intervals to children negative to tuberculin, and failed to get any false positive reactions. Next they attempted to correlate the size and intensity of the tuberculin reaction with the localization of the lesion, the activity of the lesion, and the prognosis of the case, but concluded that no proof of any correlation could be advanced. The stability of dilutions of old tuberculin was investigated. Eight out of eleven children reacted positively to a twoyear-old dilution of 1:10,000, although all of the children reacted positively to a fresh dilution. A six-month-old dilution kept outside of the refrigerator resulted in the same number of positive reactors in forty children as a freshly prepared dilution. They conclude that dilutions of old tuberculin up to 1:10,000 need not be prepared oftener than once a month and need not be kept constantly in a refrigerator.

The necessity for the use of separate syringes for tuberculin testing is indicated by an experiment which demonstrates that tuberculin is thermostable. Syringes were filled with a fresh solution of 1:10,000 of old tuberculin and the contents expelled. The syringes were boiled for five minutes, and then filled with a salt solution. Intradermal injections of 0.1 e.e. of the salt solution in twenty children resulted in positive reactions in 40 per cent of the cases. Comparable results were found when the syringes were rinsed ten times in 95 per cent alcohol and three times with normal saline solution. Contrary to the findings of certain other investigators,12 Lincoln and co-workers are of the opinion that a positive tuberculin test, especially when a diagnosis of primary tuberculosis has been established, rarely tends to become negative dur-They retested 113 positively reacting children after ing childhood. intervals of five to twelve years and found that 111 of them remained positive, and furthermore that 99 reacted to the initial dose of 0.01 mg. Since a child with a positive tuberculin test is likely to remain positive during childhood, they see no advantage in repeating the test; in fact, they feel repetition may be definitely harmful. Again differing from some other reports,13 the authors found only two negative reactions among 352 children with definite roentgenologic or clinical evidence of active or healed tuberculosis. They conclude that a negative tuberculin test is of great significance in excluding tuberculosis in children and that the association of a negative tuberculin test with a healed lesion is uncommon before 12 years of age. They compared the incidence of positive reactions at Bellevue Hospital for the period from 1921 to 1928 and for the period from 1930 to 1936, and report a marked decrease in the first year of life, as well as an appreciable decrease between the ages of 1 and 2 years, but found the percentage of reactions

for all ages had decreased only from 17.0 to 16.4 per cent.

A qualitative and quantitative comparison of old tuberculin and purified protein derivative with roentgenologic correlation on 1,003 children by Crimm, Short, and Wood<sup>23</sup> presents many interesting findings. Each patient was first tested simultaneously with 0.1 mg. of old tuberculin, and 0.00002 mg. of purified protein derivative, and five days later with 1.0 mg. of old tuberculin and 0.005 mg. of purified protein derivative. The result of tests with the first dilutions was the finding of 215 reactors. Of this number, 93 per cent reacted to purified protein derivative, and 76 per cent to old tuberculin, indicating that the former is 17 per cent more effective. With the second dosage there were 325 positive reactions, indicating a superiority over the first dose of about 33 per Of the 325 reactors, 84 per cent reacted to purified protein derivative, and 73 per cent to old tuberculin. From their study the authors conclude that purified protein derivative is 14 per cent more effective in finding tuberculosis than is old tuberculin. Furthermore, the intensity of the reaction to purified protein derivative is usually one to two degrees greater than with old tuberculin. In their opinion the strength of the second dose of purified protein derivative should be diminished. One surprising result recorded in this study, and one quite at variance with most other studies of a similar nature, was that more cases of primary tuberculosis were found in the group of 1,003 children by the x-ray film than by the tuberculin test; 345 of the children had positive x-ray findings, but 153 of them reacted negatively. The majority of the anergic cases occurred in the group from 8 to 14 years of age.

Opinion is nearly universal that the intradermal method of tuberculin testing possesses advantages which make it superior to other methods. However, circumstances may arise in which it is desirable to avoid the use of a syringe and needle. In 1937 Vollmer and Goldberger<sup>24</sup> introduced a patch test for tuberculosis which conformed with the Pirquet test in 85.5 per cent of 209 tuberculous children. Recently these authors<sup>25</sup> have increased the sensitivity of the patch test by the use of tuberculin produced from a synthetic medium which is about four times stronger than the tuberculin formerly used. In a rather small series of cases they demonstrate that the improved patch test conforms to the Mantoux test using the second strength of purified protein derivative. Steele and Willis<sup>26</sup> also found that purified protein derivative and TPT used in a strength of 10 mg, per cubic centimeter gave reactions by the Pirquet method in approximately the same incidence as does old tuberculin used intradermally. One of the surprising recommendations in the use of diagnostic tuberculin is that of Paretzky,27 who advises the use of 10 mg. of old tuberculin in selected cases. In patients with a suggestive history and suspicious physical findings who fail to react to 0.1 mg. and 1.0 mg. of old tuberculin, the use of 10 mg. not infrequently aids in establishing a correct diagnosis. The author does not recommend this dosage as a routine procedure, only for certain diagnostic problems in which repeated tests with smaller doses are negative.

Of interest in the evaluation of the tuberculin reaction is the work of Howe,<sup>28</sup> who demonstrated a marked daily variation in the reactions of four patients with pulmonary tuberculosis, and of two controls with positive reactions but no roentgenologic or clinical evidence of tuberculosis. Daily fluctuations varying from 100 to 50 per cent of the maximal reaction to the doses employed were recorded graphically. The author

points out that there is a definite correlation between the quantitative variations in the tuberculin reaction and the state of the peripheral vessels as measured by daily diastolic blood pressure levels. Periods of peripheral vasoconstriction are accompanied by decreased reaction to tuberculin. Periods of peripheral vasodilatation, with a falling diastolic pressure, are accompanied by an increased reaction to tuberculin. In the six patients studied, the trend of the tuberculin reaction was roughly parallel; this was attributed to changes in the meteorologic environment.

This year's review may be brought to a conclusion by a brief reference to another interesting study in which the use of tuberculin played a major role. Stewart,29 looking toward the eventual eradication of human sources of tuberculosis contamination, as has been accomplished by the veterinarians in the bovine family, undertook a study in which the objective was to determine an economical method for detecting households which harbored patients with cases of open tuberculosis. points out that the ideal and complete method for controlling tuberculosis in man should include, "first, the routine application of the Mantoux test to the present and future members of the entire population; second, periodic retesting of all persons found uninfected on previous surveys; third, frequent roentgenologic, clinical and laboratory examinations of each infected patient discovered during repeated epidemiologic surveys; and fourth, prompt segregation of all patients with tuberculosis until their condition is no longer infectious." While such a program is ideal and not altogether impossible of attainment, it is obvious that for many reasons, the most important of which is economic, little prospect exists of even partial realization of this ideal approach to the control of tuberculosis.

A substitute method is suggested, therefore, which is both economical and practicable; one which, if generally participated in by the practicing physicians of the country, would constitute an epidemiologic control program for tuberculosis among human beings comparable to that which has been established by veterinarians for animals. The economic expedient proposed hinges upon the assumption that any adult members of a household who are sources of contagion will infect the children of that household. Hence, when the Mantoux tests of the children of a family are negative, it can be assumed, even if one or more adults have positive reactions, that the adult positive reactors are not spreaders of tubercle bacilli at that time, and, therefore, relatively expensive roent-genologic, clinical, and laboratory examinations for this group may safely be deferred. All such households can be safely accredited as contagion-free units solely upon the results of the Mantoux tests. Only in those households where one or more of the children react positively to the tuberculin test is it imperative that the infected adults (as shown by positive Mantoux tests) receive these additional examinations.

In a practical demonstration of his plan, Stewart investigated, wholly or in part, the personnel of 642 homes. Approximately 57 per cent of the parents and 84 per cent of the children were given the Mantoux test. Positive tests were found among 57.3 per cent of the parents, and 5.2 per cent of the children. From this and other data obtained in the study, the author concludes that "primary tuberculosis, the type or stage of the disease that is present in each tuberculin-sensitive patient, is a relatively unimportant source from which infection in man is acquired by contact. Apparently efforts to control the human source

of the disease can be concentrated almost exclusively on the identification and segregation of patients with the ulcerative or reinfection type of pulmonary tuberculosis.' The entire personnel of 213 of the 642 homes was given the tuberculin test. Forty-two of these households did not contain an infected member, and, in 149 more, tuberculin sensitivity was limited to the adult members of the family. Thus 191, or 89.7 per cent, of the completely tested units were tentatively rated as safe for children to live in, this rating being made solely on the basis of the reaction to tuberculin. In the remaining 22 households, the infected members received roentgenologic, clinical and laboratory examinations. The source of the child's infection in only 2 instances was found to be among the 22 homes.

In the present confused state regarding the relative merits of various types of case-finding surveys. Stewart's proposal deserves careful consideration. Sooner or later the futility of haphazard tuberculin surveys, particularly those limited to grade school children, as a means of detecting unknown cases of open tuberculosis, must be recognized. Ultimate success in the epidemiologic control of tuberculosis would seem to depend upon the general adoption of some systematic method of investigation which would eventually include the majority of the people in a given community. It is conceivable that a program aimed at the accrediting of homes, then of counties, and finally of states, might be found as feasible for man as the similar approach has been for animals.

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704 EQUITABLE BUILDING

# American Academy of Pediatrics

# Proceedings

# EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 10 AND 11, 1938

Round Table Discussion of the Teaching of Body Mechanics in Pediatric Practice

Chairman, Dr. Clifford Sweet, Oakland, Calif. Assistant, Dr. Herbert E Coe, Seattle, Wash.

CHAIRMAN SWEET.—A clear understanding of the mechanics of the human body in rest and in motion must rest on certain fundamentals:

- 1. The body is subject to the laws of gravity, and maintenance of good posture with the least muscular effort demands that the body be arranged, as nearly as possible, symmetrically about a vertical line passing through the body's center of gravity. In other words, to maintain the upright posture each part of the body must be counterbalanced by another part with an equal moment of force (moment of force: mass × horizontal distance from the center of rotation) or by muscular con traction sufficient to balance the inequality. This indicates clearly that, when for any reason some part of the body is extended too far from the center of gravity in a horizontal direction, another part will be extended too far in the opposite horizontal direction to restore balance, adjusted by the semicircular canals to maintain the visual plane parallel to the earth's surface.
- 2. All skeletal muscles are arranged in pairs as antagonists: for every flevor there is a corresponding extensor. These antagonistic muscles are at rest only when they are simultaneously relaxed, which is possible only when the part which they move or support is in equilibrium. Any muscle which has the linear distance between its origin and insertion shortened takes up the slack thus allowed and increases both in cross section and strength, while any increase in length or stretching produces a corresponding decrease in strength, with a corresponding decrease in cross section. In general the strength of a muscle varies directly with its cross section and indirectly with its length. Any advantage which a muscle gains over its opponent increases steadily—the strong muscle gains and the weak muscle loses strength-thereby increasing the departure from equilibrium, with the production of increasing deformity. Certain muscles, because of their great strength and because they are shortened when the body is in a habitual incomplete upright posture, in a long continued sitting posture, especially if slumping is added, or in an in correct lying posture, are most frequently able to gain and increase their advantage over their opponents. In general, those are the muscles which were of greatest use when our ancestors traveled on all fours and those which must exert the most force in maintaining the active equilibrium of the body in the present upright posture. The props and pectoral muscles are an example of the first group and the gastroc nemius of the second.

- 3. All deformities, with the exception of those apparent ones which represent a stage of development in the growing child, tend to increase. The reasons for this increase are as follows: The deformity allows the shortening and therefore the gain in strength of muscles over their opponents; growth takes place in the direction of use (Wolff's law); any posture or method of movement tends to become implanted in the kinesthetic sense as a habit; generally it is easier and more comfortable to rest and move with a deformity than against it toward correction, and in the young, growing child with his elastic tissues and his great skill for learning new, substitute stances and movements, deformities, even though considerable, rarely cause sufficient discomfort to make their correction mandatory.
- 4. Ontogeny recapitulates phylogeny in the development of body mechanics as truly as in other aspects of growth and development. Every child must learn to sit up, to stand upright, and to walk and run as a biped. His level of skill may stop at any of the stages leading toward perfection in these skills as truly as it may in music or mathematics. Beethoven's Fifth Symphony is not for beginners, and higher mathematics does not yield to the multiplication tables alone.

As in all other development of the human being, heredity and environment have the principal roles. Heredity determines the quality of the body with which he begins life and the energy or "spirit" which will give him the urge "to strive forward toward perfection in all things," while environment contributes the conditions which will aid him in his upward struggle or place obstacles in his path. The ideal environment is that which enables him to make the most of his hereditary possibilities. Skill in standing, walking, running, sitting, and relaxation, all of which are so useful in everyday living and a lack of which allows so much injury to the body, surely is of sufficient importance to warrant one's best efforts as teachers of parents and children.

Six cases were presented demonstrating varying postural defects.

Dr. Coe in discussing the first case stated that the shortening of the hamstring muscles keeps pelvis rotated improperly, that the short posterior group may be due to ballet dancing which prevented proper dorsiflexion. Exercises and not Thomas heels are needed to correct this condition.

DR. WILLIAM WESTON (COLUMBIA, S. C.).—Do you find that children who do toe dancing exaggerate the sway back and failure of flexion?

CHAIRMAN SWEET.-Yes, but I have no objection to walking on toes.

Dr. Coe in presenting second case emphasized the fact that this boy, aged 12 years, presented a pelvis rotated forward, with increased lumbar lordosis and mild hyperextension of knees, and suggested, as an exercise for short heel cords, that the patient kneel slightly with feet on floor and feet parallel.

DR. G. M. CULTRA (AMARILLO, TEXAS).—What do you think of having child lying down with knees flexed and then trying to sit up?

CHAIRMAN SWEET.—The rectus muscles do not have much to do with posture. I am more interested in the oblique abdominals. I feel that the recti will take care of themselves. I divide the body into two kinds of structures, those that support weight and the others that are carried about as passengers. I cannot walk or work with chest up and rectus tight; it is not natural to hold abdomen in uncomfortably.

DR. W. A. McGEE (RICHMOND, VA.) .- How often do you advise exercises?

CHAIRMAN SWEET.—Five minutes night and morning and a mattress that supports the body horizontally during sleep.

DR. H. R. LUSIGNAN (MONTEREY, CALIF.) .- Would toe dancing be contra-indicated?

CHAIRMAN SWEET.—No, but I would give foot exercises and recommend walking pigeon tood; our job is to keep the feet strong and balanced.

DR. G. B KRYDER (Los Angeles).—What are the contraindications to going barefoot?

CHAIRMAN SWEET -None, except rattlesnakes; give the children freedom and an opportunity to use their feet.

DR. KRYDER -- What about Keds?

CHAIRMAN SWEET .- Keds, if ventilated, are good.

DR. KRYDER —I had a patient who used Keds for jumping; he awoke each morning with pains in his feet, but on changing to shoes with heel this disappeared

CHAIRMAN SWEET—High jumpers use a heeled track shoe. I formerly thought that Keds were detrimental, but now I do not feel so about them A corn on the little toe indicates that the shoe does not fit snugly in the heel

DR. KRYDER.—At what age do you begin exercises?

CHAIRMAN SWEET—This is covered in the charts. If the child has a very weak foot put on heel shoe at about 15 months

DR. EDITH BOYD (MINNEAPOLIS, MINN),-Why wear heel at all?

CHAIRMAN SWEET.—Because it is easier to balance on the center of gravity if one wears heels. The tendency for most people is to drop back on the heels.

DR. McGEE .- Do you like the moccasin shoe?

CHAIRMAN SWEET .-- Yes, I do.

GUEST IN AUDIENCE -What is wrong with a shoe that causes a bumon to develop?

CHAIRMAN SWEET.—Too short a shoe Avoid rigid soled shoes or too short shoes from the onset.

DR. E. G. SCHWARZ (FORT WORTH, TEXAS) —What do you think of Taylor Tots or other devices as causative factors?

CHAIRMAN SWEET.—I do not feel that a child stays in a walker long enough to do any harm. I think that brings up a problem of child psychology. I am trying to teach mothers to keep the child sheltered and protected while he is busy, but later to devote considerable pleasant attention to the child.

MRS. OSCAR REISS (Los Angeles, Calif.).—With preschool child is it neces sary to fit the chair to the child?

CHAIRMAN SWEET.—I feel that to keep a child in a chair that is too large for him is bad, otherwise not, if there is only a slight variation.

DR. LANGLEY PORTER (SIN FRANCISCO).—Give a child activities that teach him to reach above his head; this will give strength to upper trunk. I feel that the barefoot child has a strengthened foot and that slow walking is frequently due to heavy bedelothes, causing foot drop.

CHAIRMAN SWEET.—I dislike all shoes with corrections early in life; I have no objection to a little lift at the heel, not in the sole. I feel that a shoe should not interfere with the flexion of the foot.

DR. LUSIGNAN .- Does not the Thomas heel make children grasp with the toes?

CHAIRMAN SWEET.—Yes, I think it does to a certain extent. However, if the foot is in a shoe with a rigid shank and rigid sole, not much can be done in the way of grasping.

DR. LUSIGNAN.-Why do obstetricians advise mothers to wear low broad heels?

CHAIRMAN SWEET.—I think to increase the stability primarily, particularly in walking. If the expectant mother is taught to stretch her posterior leg muscles, she can wear the low broad heel comfortably and with permanent advantage.

DR. E. J. BARNETT (SPORANE, WASH.).—Would you like to say what brand of shoes you would prefer for young children?

CHAIRMAN SWEET.—I do not wish to advertise any particular brand of shoe. There are several excellent makes of shoes, many of which I am not acquainted with. My minimum requirements for a shoe are that it be made on a combination last, since all children have combination feet; that it be sufficiently flexible for the child to walk in it easily; and that it fit the child's foot.

DR. JACOB WALLEN (PHILADELPHIA).—How about shoes for infants who are just learning to walk?

CHAIRMAN SWEET.—I prefer to have children who are just learning to walk go barefooted at least part of the time. When shoes are worn, I think they should be flexible, of the soft moccasin type.

DR. LUSIGNAN.—Do you ever attempt to keep the heavy child from early weight-bearing by using a walker?

CHAIRMAN SWEET.—I have not attempted to prevent weight-bearing by the use of a walker. I think, in general, one may quite safely let the child follow any activity which his own abilities can support.

DR. J. R. LEMMON (AMARILLO, TEXAS).—Will you say something about the bandy-legged child and what corrective measures you would advise?

CHAIRMAN SWEET.—Any child who has any deformity should first be carefully examined. For example, Dr. Lemmon, the type of child you refer to may have calf muscles that are too long and need heeled shoes. He may have weak or poorly developed abdominal muscles, or he may need particular attention to his gluteal muscles in order to strengthen and develop the external rotators of the femurs.

DR. N. L. MOORE (SANTA ANNA, CALIF.).—Do sleeping posture and the type of mattress play a part?

CHAIRMAN SWEET.—Sleeping posture and the type of mattress do play a part in the development of children. A mattress should be firm and should be supported in a horizontal manner either by efficient springs that are tied together diagonally or by boards placed between the spring and the mattress.

DR. HUGHES KENNEDY, JR. (BIRMINGHAM, ALA.).—Can you get a 4-year-old child to cooperate with exercises. I have in mind a child with flat feet and leg pain.

CHAIRMAN SWEET.—Yes, I think a 4-year-old child will cooperate with exercises, provided that they are presented in the form of a game. For example a child will raise himself from the prone to the sitting position, thereby using the abdominal muscles many times, provided that someone does it with him and calls it a game. The child you describe with leg pains should be checked over to see whether or not be has abnormally long or short muscles.

Dr. Edwin G. Schwarz, Secretary Fort Worth, Texas

## News and Notes

The committee in charge of the Fifth International Congress of Pediatrics, which will convene in Boston and Cambridge, Mass., Sept. 2, 3, 4, and 5, 1940, announces the following tentative program:

Monday, September 2-

Registration.

Business Meeting of National Committees of Congress.

Tuesday, September 3-

Harvard University, Cambridge, Mass.

A.M. Referat: Deficiencies of the Vitamin B Complex.

P.M. Discussion-4 selected subjects.

Wednesday, September 4-

Harvard Medical School, Boston, Mass.

A.M. Sectional meetings.

P.M. Scientific exhibits, excursions, and sports.

Thursday, September 5-

Harvard University, Cambridge, Mass.

A.M. Discussion-4 selected subjects.

P.M. Referat: Viruses in Relation to Disease in Infancy and Childhood.

Evening-Banquet.

Representative pediatricians from various countries will participate in the referats and discussions at the general assemblies. Individuals desiring to submit papers either for the general or sectional meetings should do so through the national committee of the country they represent. Each title sent by the various national committees to the general secretary must be accompanied by an abstract not in excess of 300 words of the material to be presented.

There will be four official languages for the Congress, English, French, German and Italian. The choice of these languages in which the papers may be presented will be left to the discretion of the essayist. At the general sessions of the Congress a translation system will be installed with earphones at each seat. While the speaker is presenting his data, translators will repeat what he says in the other Congress languages so that the listener may hear the speech in any one of these languages which he prefers.

Arrangements are being made for scientific exhibits and for excursions to points of medical interest in and about the city; while the women's committee are making special arrangements for the entertainment of women members of the Congress as well as for the wives of the participating members.

## THE JOURNAL OF **PEDIATRICS**

## A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Official Organ for The American Academy of Pediatrics

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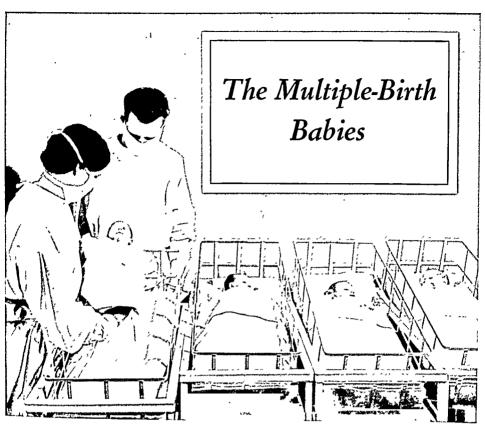
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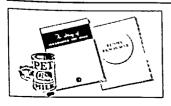
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## A Word

## About the Balkan Medical Union

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It is through the "Medical Weeks" that our Balkan Union tends to realize these aspirations.

Athens, Belgrad, Bucarest, and Istanbul, each in turn have seen more and more numerous and enthusiastic groups come together, all permeated by the same desire of comprehension and friendship. We doctors know that a very small quantity of vaccine can protect millions of men from the danger of contagious diseases. So the good seed scattered by the Balkan Medical Union is a real remedy against the evils set loose by human passion.

Prof. Dr. Akil Moukhtar Ozden.

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## Your Infant Feeding Problems

Pediatrics consists very largely in solving feeding problems. Possibly no man in pediatrics has contributed so much to the correct solution of these problems as the late Dr. Williams McKim Marriott. Fortunately he has left a record of this work in the last edition of his book, published just one year before his death.

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Fig. 3.—Xerophthalmia, the result of a diet deficient in vitamin A.

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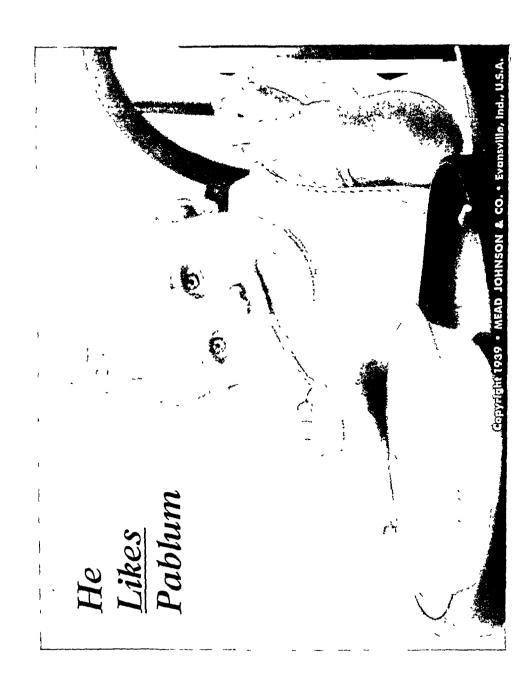
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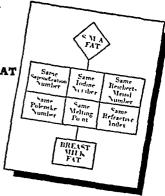
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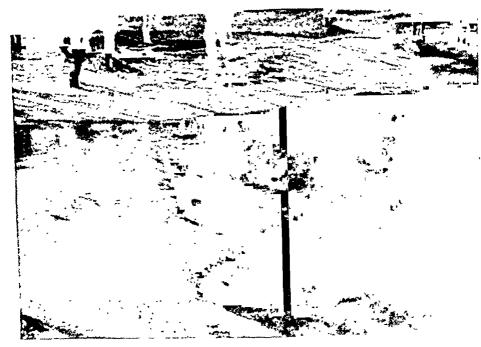
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		120 cals.
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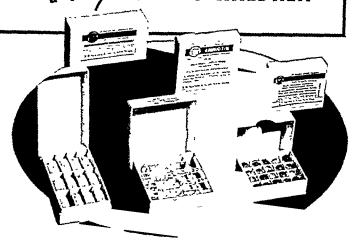
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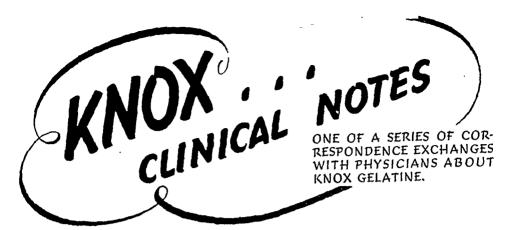
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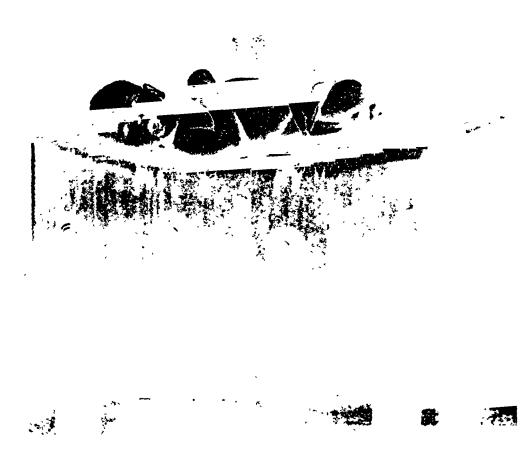
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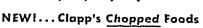
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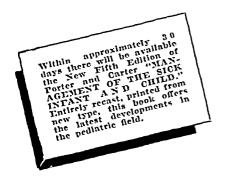




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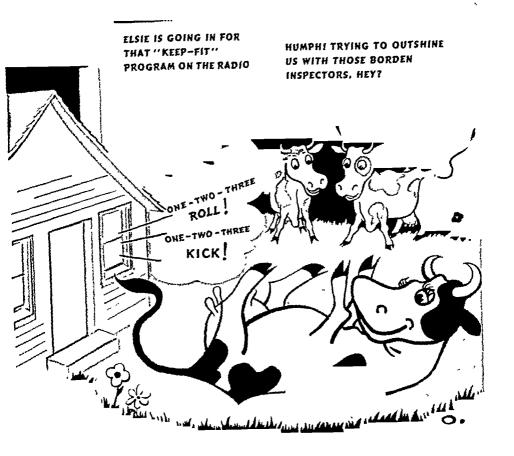
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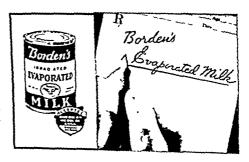
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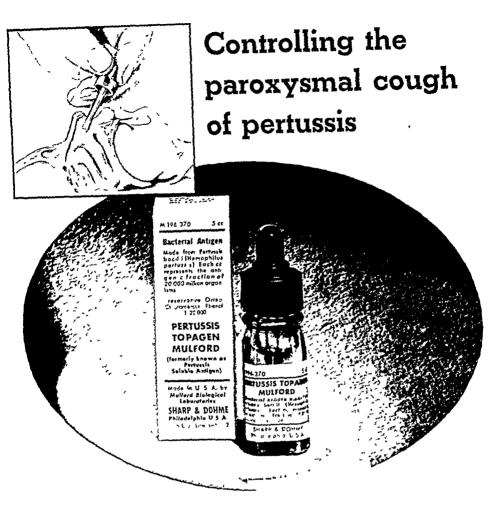
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\*Taulkner, J. M., and Taylor, F. H. L. Ann. Let. Med. 13 1867, June 1937

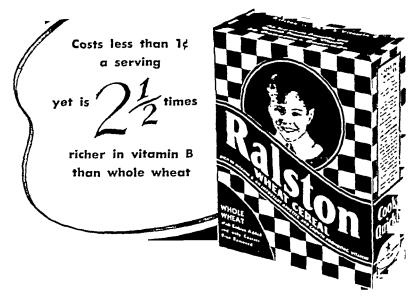


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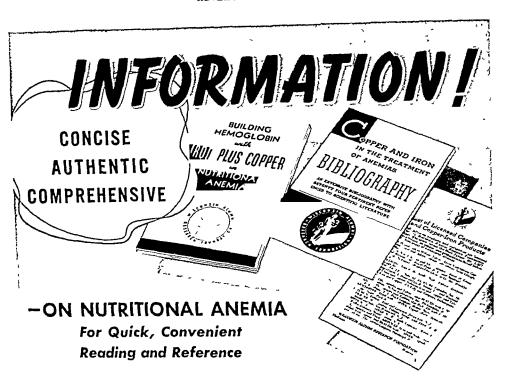
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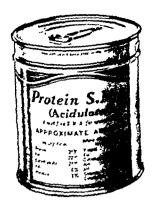
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(1) Gerstenberger, H. J., and Nourse, J. D., "The Prevention of Rickets in Premature Infants," Jr. A.M.A., Vol. 87, pp. 1108-1114

(2) Horesh, A. J., and Russell, G. R., Observations on the Growth and State of Nutrition of Premature Infants Given an Antirachitic and Antiscorbutic Lood." Olio State Medical Journal, May, 1935

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Inhaltsübersicht: Allgemeiner Teil: Anatomischer Aufbau der Haut im Kindesalter. Von Professor Dr. J. Becker, Bremen. — Stoffwechsel und Immunbiologie der Haut. Von Professor Dr. P. György, Cambridge (England). — Allgemeine therapeutisch-technische Hinweise. Von Geh. Rat Professor Dr. L. v. Zumbusch, München. — Spezieller Teil: Angeborene Fehlbildungen der Haut. Von Dr. K. Steiner, Wien. — Geschwülste der Haut. Von Professor Dr. W. Scholtz, Königsberg. — Pigmentanomalien, Xantome und Schüller-Christiansches Syndrom, Recklinghausensche Krankheit. Von Privatdozent Dr. W. Jadassohn, Zürich. — Hautveränderungen bei Leukämien, Lymphogranulomatose und Erkrankungen verwandter Art. Von Professor Dr. O. Ullrich, Essen. — Hautveränderungen bedingt durch Störungen am peripheren Gefässapparat. Von Dozent Dr. St. R. Brünauer, Wien. — Anomalien und Erkrankungen des Taig. und Schweissdrüsenapparates. Von Professor Dr. R. O. Stein, Wien. — Zoonosen. Von Professor Dr. O. Kiess, Leipzig. — Pilzerkrankungen (Mykosen) im Kindesalter. Von Professor Dr. A. Buschke, Berlin und Dr. A. Joseph, Berlin. — Pyodermien und bakterielle Hauterkrankungen verwandter Art. Von Professor Dr. O. Ullrich, Essen. — Herpes. Von Dozent Dr. H. Lehndorff, Wien. — Ekzem und ekzemähnliche Dermatosen. Von Geh. Rat Professor Dr. H. Finkelstein, Berlin. — Urticariagruppe. — Erythemkrankheiten im Kindesalter. Von Dozent Dr. H. Lehndorff, Wien. — Pemphigus. Von Geh. Rat Professor Dr. L. v. Zumbusch, München. — Die Epidermolysis bullosa hereditaria. Von Professor Dr. J. K. Mayr, Münster. — Keratosen. Von Professor Dr. C. Moncorps, München. — Erkrankungen der Haare und Nägel im Kindesalter. Von Professor Dr. C. Stein, Wien. — Pesoriasis vulgaris. — Lichen ruber. Von Professor Dr. O. Kiess, Leipzig. — HautDiphtherie. — Vaccinosen. — Exanthematische Formen der Hauttuberkulose im Kindesalter. Von Professor Dr. W. Keller, Mainz. — Lepra oder Aussatz. — Pellagra. — Lupus vulgaris. — Unon Professor Dr. C. Moncorps, München. — Sa

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### Original Communications

### INCLUSION BLENNORRHEA

WILLIAM ALLEN HOWARD, M.D. WASHINGTON, D. C.

INCLUSION blennorrhea is a chronic, nonbacterial form of conjunctivitis occurring in the neonatal period, and is thought to be due to the activity of a specific filterable virus. It is not a new disease but has received increasing recognition through recent researches concerning its etiology. It comprises about 10 to 20 per cent of the cases of ophthalmia neonatorum seen in hospitals, where gonorrheal ophthalmia is becoming a rarity. Published reports have been confined to the ophthalmologic periodicals; thus it would seem desirable to bring this entity to the attention of pediatrists, among whom it frequently goes unrecognized.

### HISTORICAL

Morax' in 1903 recognized a benign form of purulent ophthalmia in the newborn, unassociated with any pathogenic bacteria. He thought the conjunctival inflammation, like "snuffles," might be a manifestation of hereditary syphilis. Later, in 1909, Heymann<sup>2</sup> discovered epithelial inclusions, similar to those found in trachoma, in stained smears of the conjunctival secretions of these cases. Morax, Lindner, and Bollack<sup>3</sup> in 1911 confirmed this work, but were unable to determine the origin of the inclusions. The name "Einschlussblennorrhöe" or Inclusion Blennorrhea was applied to the condition by Lindner,

Since this initial work, many theories have been propounded concerning the etiology of the inclusions. Lindner considered them to be intracellular groups of the causal organism. Stewart<sup>5</sup> concluded that inclusion bleunorrhea was not a separate entity, but merely gonorrheal

From the Department of Pediatries, University of Rochester School of Medicine and Dentistry and the Strong Memorial and Rochester Municipal Hospitals, Rochester, N. F.

ophthalmia, and stated that the inclusions were only clumps of phagocytosed gonococci. Lumbroso<sup>c</sup> considered the inclusions to be reaction products of the cells to a filterable virus. The work of McKee<sup>7</sup> had led him to the belief that the inclusions are formed by phagocytosis of bacteria which are not the cause of the disease, but which may carry the virus. Thygeson<sup>s</sup> has reported a series of experimental studies which

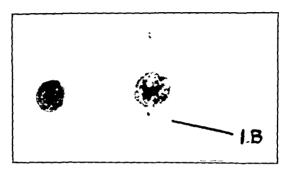


Fig. 1.—I.E., initial body contained in the cytoplasm of an epithelial cell (×970).

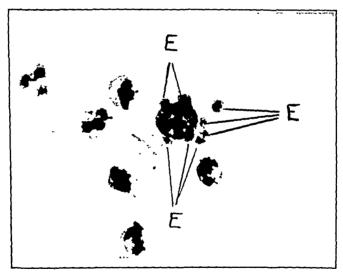


Fig. 2.—E, numerous clusters of elementary bodies contained within the cytoplasm of a single epithelial cell ( $\times 970$ ).

lead him to conclude that the cytoplasmic inclusion bodies constitute intracellular colonies of a specific filterable virus in various stages of development.

#### **ETIOLOGY**

Thygeson believes the etiologic agent of the disease is a filterable virus having an elementary body phase and an initial body phase. In preparations of the secretion from acute cases of inclusion blennorrhea

stained by a modification\* of the Giemsa technique, both phases may be found included in the leucocytes and epithelial cells. The elementary bodies may also be found extracellularly. The initial bodies are coccobacillary in shape, ranging from 0.3 to 0.8 microns in greatest diameter. They stain blue and usually more intensely at the poles. The elementary bodies are smaller, sharply defined granules, averaging 0.25 microns in diameter, occurring singly and in clusters of varying size. They stain reddish blue. All forms of the inclusion bodies may be found in an ordinary Giemsa-stained smear of the conjunctival secretions, but are much more readily identified in preparations of epithelial scrapings from the conjunctiva. Both initial and elementary bodies show up well



I'ig. 3.—N, nucleus of epithelial cell L, single cluster of elementary bodies indenting the nucleus, but without destruction of the nuclear membrane (×970).

in the pale staining cytoplasm of epithelial cells. The intracellular clusters are quite typical in appearance, but the free forms, even when numerous, are more difficult to identify.

The etiologic significance of these bodies was indicated by a carefully controlled series of experiments performed by Thygeson, the results of which he summarized as follows:

- 1. Constant presence of the inclusions in the disease.
- 2. Absence of inclusions in conjunctivitis of known bacterial origin.

<sup>\*</sup>The usual technique for the Giemsa stain is followed. The slide is kept in the solution approximately twenty minutes, in a perpendicular position to prevent precipitation. The slide is removed, washed with water, then passed through two washes of five seconds cach in 95 per cent alcohol. This serves to decolorize the acidophilic and neutrophilic granules in the cells, thus making the inclusion bodies, which are alcohol fist, stand out more clearly.

- 3. Absence of pathogenic bacteria in inclusion blennorrhea, and the failure of occasional saprophytes present to produce the disease when used for inoculation.
- 4. Multiplication of the elementary and initial bodies in the new host when the disease is transferred to the normal human conjunctiva.
- 5. Production of the disease with bacteria-free suspensions of elementary bodies.
  - 6. Filtrates not containing elementary bodies are not infective.

Observations made from experimental transmission of the infection have led Thygeson to postulate the existence of a forty-eight-hour life cycle for the virus. As observed in the experimentally inoculated susceptible host, the transition from the elementary body phase, through the

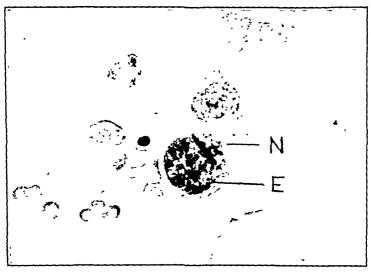


Fig. 4.—E, large cluster of elementary bodies, practically filling the epithelial cell. N, nucleus, compressed and partially destroyed by the growing virus colony  $(\times 970)$ .

various forms of the virus, to the development of new elementary bodies, requires approximately forty-eight hours. From the examination of smears made at regular intervals during this period, the various stages of development of the virus may be accurately determined. The elementary body enters a cell and finding suitable nutrient material, develops into an initial body. This in turn divides and forms the mulberry mass or cluster of new elementary bodies, this large inclusion body usually capping the nucleus. The nuclear membrane then becomes weakened, ruptures, and the elementary bodies fill the entire cell. Due to internal pressure or external trauma, the cell then ruptures with discharge of the elementary bodies. These may then take up their abode in new cells. This explanation agrees closely with the observations of Bedson on the life cycle of the virus of spittacosis.

Opinion, however, is not unanimous concerning the etiology of this condition. McKee,<sup>7</sup> in his study of 27 cases of purulent ophthalmia in the newborn, found epithelial cell inclusions alone in 8 cases, while in as many more instances the inclusions were found associated with the gonococcus. In one instance inclusions were present in a streptococcic conjunctivitis. As previously mentioned, McKee believes that the inclusions are made up of phagocytosed bacteria. The apparent occurrence of cases of pure inclusion body conjunctivitis is explained as being due to the admitted difficulty in proving the presence of organisms in all cases. He later states, in referring to the inclusions of trachoma, swimming bath conjunctivitis, and inclusion blennorrhea, that while the inclusions are undoubtedly due to phagocytosed bacteria, these bacteria may not be the cause of the disease, but may carry the virus if such is the causal agent.

Clapp, in discussing a report by Thygeson and Mengert's on the properties of the virus of inclusion blennorrhea, states his belief that the inclusion bodies probably represent a cellular reaction rather than a stage in the development of the virus.

Thygeson believes that the epidemic form of swimming bath conjunctivitis represents the adult infection with the virus of inclusion blennormea.

Gifford and Lazar<sup>10</sup> tried to produce inclusions in the conjunctival epithelium of newborn infants by the application of a 2 per cent infusion of senega. Three of the 26 infants developed inclusions. Repeating this work on a series of 27 infants, they were unable to duplicate their findings. As a result of their experiences they assumed that the virus of inclusion blennorrhea was present in a latent form, and activated by the presence of a chemical irritant.

While Thygeson's work has not been completely accepted, a more satisfactory explanation of the etiology of inclusion blennorrhea has not been offered.

During the six months from January 1 to July 1, 1937, 30 eases of purulent ophthalmia in the newborn were observed on the obstetric and pediatric services of the Strong Memorial and Rochester Municipal Hospitals. Cultures and smears were made in each instance to determine the etiology, in an attempt to confirm the bacteriologic findings of Thygeson.

All inoculations were made on Bradford's\* medium, which was found to be an excellent culture material for all the conjunctival organisms, pathogenic and nonpathogenic, including the gonococcus. In all doubt-

<sup>\*</sup>Brudford's medium is made using 100 c.c. of 2 per cent Douglas agar of pH 7.6 to 7.8, to which has been added 25 c.c. of sterile ascitic or hydrocele fluid, 5 c.c. of a sterile 20 per cent solution of glucose, and 10 c.c. of sterile defibrinated rabbit's blood. The mixture is poured into sterile Petri dishes,

ful cases, special gonococcus cultures were made on chocolate agar plates and incubated in scaled glass jars containing 8 to 10 per cent of carbon dioxide.

TABLE I

ORGANISM	NUMBER OF CONTAINING CASES CLUSIONS				
Hemolytic staphylococcus	15	0			
H. influenza	( 3	0			
D. pneumoniac	2	0			
Hemolytic para-influenza	1	0			
Streptococcus homolyticus	1	0			
Nonpathogens (diphtheroids and non- hemolytic staphylococci)	3	3			
No organisms isolated	5	4			
Totals	30	7			

Of the 30 infants examined, a bacteriologic diagnosis was possible in 22. In none of these were inclusions found in the Giemsa-stained smears. Intracellular groups of organisms were frequently seen in the bacterial cases but they in no way resembled true inclusion bodies as found in the nonbacterial cases. In 8 infants cultures were either sterile or grew only the nonpathogenic diphtheroids and nonhemolytic staphylococci. Seven of these 8 cases showed typical cytoplasmic inclusions in successive preparations of conjunctival secretions stained by the Giemsa method. In the eighth case, no etiologic agent was determined. This may represent a failure to isolate the causal organism, or the inclusions may have been missed. No ease of gonorrheal ophthalmia was seen.

These bacteriologic findings tend to substantiate Thygeson's statements that true cytoplasmic inclusions do not occur in conjunctivitis of known bacterial origin, and that pathogenic bacteria are not found in inclusion blennorrhea.

#### PATHOLOGY

Thygeson<sup>s</sup> has reported the examination of tissue sections in one case of inclusion blennorrhea. The sections were taken through the upper fornix, and revealed a dense subepithelial infiltration with all types of inflammatory cells, chiefly plasma cells. No folliele formation was noted, though it has been seen in experimental infections in adults and in the baboon. The epithelium was infiltrated with polymorphonuclear leucocytes, and in the superficial layers an occasional cytoplasmic inclusion body was seen.

#### IPIDEMIOLOGY

The fact that inclusion blennorrhea characteristically occurs in the newborn infant naturally led to the suspicion that it was transmitted during passage through the birth canal, as in the case of gonorrheal ophthalmia. Vaginal discharge has been a frequent finding in the mothers of these infants. Examination of cervical smears stained by

the Giemsa method has shown the presence of typical inclusions in the epithelial cells. Thygeson and Mengert<sup>9</sup> found inclusions in the cervical epithelium of 7 of 9 mothers of infants with inclusion blennorrhea. They also report an instance in which a gynecologist became infected accidentally during the performance of a dilatation and curettage. This infection ran a course typical of inclusion blennorrhea in the adult. The patient upon whom the operation was performed was examined three months later but at that time no inclusions could be demonstrated in cervical smears.

These investigators also searched for evidences of an inclusion infection in the urethras of male patients. In 11 cases of nonspecific urethritis, inclusions were found in one instance. The urethritis in this case healed after a duration of seven months.

In the present series of cases cervical smears were obtained from only one mother. Diligent search revealed 2 or 3 cells appearing to contain initial bodies. Other slides were not available to make more certain of their presence.

Transmission from one infant to another has not been observed; however, in the obstetric nursery it is the custom to isolate all cases of purulent ophthalmia when first observed. In one instance in this series, inclusion conjunctivitis occurred in one of a pair of twins. At the end of five months, the conjunctivitis was still active, while the other twin remained completely free of the disease.

There is no permanent local immunity since reinfection can be readily obtained in the experimental transmission of the disease to baboons. The virus confers no general immunity as shown by the lack of neutralizing antibodies or agglutinins for the elementary bodies in the blood of infected individuals.

#### CLINICAL FEATURES

The incubation period appears to be between five and ten days. As a rule, the onset of symptoms is usually between the seventh and tenth days of life. At first there may be only moderate reddening of the conjunctiva with the appearance of a small amount of purulent secretion at the inner canthus of the eye. It may be unilateral at the onset but always spreads to involve the other eye. Many cases remain relatively mild, the inflammation involving chiefly the conjunctiva of the lower tarsal plate.

In the more severe cases the condition takes on the appearance of an acute ophthalmia, with swelling and redness of the cyclids, intense, beefy redness of the palpebral conjunctiva, injection of the bulbar conjunctiva, and a profuse purulent discharge. The palpebral fissures are tightly closed. There is occasionally noted a tendency to the formation of a pseudomembrane on the conjunctiva. Clinically it may be impossible to differentiate this condition from a gonorrheal ophthalmia.

True follicles are not seen, but a papillary conjunctivitis is common. Corneal ulceration does not occur in neonatal inclusion blennorrhea, nor are there any vascular changes at the limbus such as are found in trachoma.

In spite of the frequent severity of local manifestations, systemic reactions have not been observed in these infants, nor has there been any evidence of spread of the infection to the other orbital structures.

#### COURSE AND PROGNOSIS

Under appropriate management the acute manifestations usually subside in a few days. The eyes lose their swollen reddened appearance and the discharge lessens considerably, but the beefy redness of the conjunctiva may persist for weeks. During this period the inclusions are still present, their numbers decreasing as the eyes improve. For months there may persist a moderate injection of the conjunctiva with a small amount of purulent material collecting at the inner canthi and along the lid margins. The inclusions become increasingly more difficult to find, and it has been noted that mild symptoms may persist after the smears have been repeatedly negative.

There are no recognizable complications or sequelae in inclusion blennorrhea, and after a period which may last several months, all signs disappear. None of the cases reported here have been observed for a sufficient length of time to make definite statements in this regard, but all are progressing satisfactorily after periods of activity ranging from two to six months.

#### DIAGNOSIS

Diagnosis can only be established definitely by the discovery of typical inclusions in Giemsa-stained preparations of the conjunctival secretion. Cultures from cases of inclusion blennorrhea are either sterile, or show only those bacteria which are known to be nonpathogenic to the conjunctiva, namely, diphtheroids and nonhemolytic staphylococci. An exception to this statement occurs in an occasional case in which a double infection or secondary infection is found. In such instances, both inclusions and a pathogenic bacterium may be found. Appropriate treatment will climinate the latter, while the inclusion blennorrhea persists and follows its usual chronic course.

In any case of purulent ophthalmia, inclusion blennorrhea may be suspected when repeated cultures and smears have failed to show any pathogenic organisms. The mild irritative chemical conjunctivitis occurring during the first two or three days of life should cause little difficulty in differential diagnosis. Differentiation from gonorrheal ophthalmia or from a purulent ophthalmia due to one of the usual conjunctival pathogens is almost impossible from symptoms alone. Re-

peated smears and cultures of the conjunctival secretions, and the use of the Giemsa stain will make an accurate diagnosis possible in the majority of cases of ophthalmia neonatorum.

#### TREATMENT

Because all forms of the so-called ophthalmia neonatorum are similar in appearance, the usual treatment for gonorrheal ophthalmia is instituted when symptoms first present themselves. Whenever the diagnosis of inclusion blennorrhea is made, therapy should be modified somewhat. All the common ophthalmic antiseptics, both liquids and ointments, have been shown to have no influence on the course of this disease; on the contrary, one will occasionally find that symptoms are aggravated by too active treatment.

In the absence of any known specific therapeutic agent, treatment should be directed at symptomatic relief of the acute manifestations and prevention of secondary infection. With this in mind the following form of management is suggested. In the acute stage cold boric compresses are applied to the eyes for a few minutes every two or three hours. After compressing, the eyes are gently irrigated with boric acid solution, using a rubber ear syringe. Irrigations are followed 2 or 3 times daily by the instillation of 2 drops of 1 per cent mercurochrome (aqueous solution) into the conjunctival sac of each eye. This treatment is continued for the duration of the acute symptoms.

When swelling and redness of the lids have diminished or disappeared and the discharge has lessened, compressing is discontinued. Boric acid irrigations are continued 2 or 3 times daily, followed by the instillation of mercurochrome. When the infant is discharged from the hospital, the mother is instructed in the manner of giving irrigations, and is told to continue them as long as signs persist. Mercurochrome is also best continued at home, at least for a short period.

After six or eight weeks of this regime, the eyes appear almost normal to casual inspection. Examination will reveal a moderate injection of the conjunctiva, with the collection of a small amount of exudate at the inner canthi and along the lid margins. In this stage, the disease then persists until its course is run.

Probably the mechanical cleansing with boric acid is the most important factor in caring for this condition. Mercurochrome serves to prevent secondary infection, although other mild antiseptic solutions will serve the same purpose. There seems to be no indication for the application of silver nitrate to the lids; rather, one should seek to avoid all trauma to the conjunctiva. The danger of argyria should always be remembered in the long continued use of silver preparations.

In those cases beginning unilaterally, one may expect the opposite eye to become affected within a few days. The severity of involvement of the other eye may be greatly lessened by using the irrigations and instillations in both eyes.

#### SUMMARY

Recent researches indicate that inclusion blennorrhea is a specific, nonbacterial form of conjunctivitis due to the activity of a filterable virus. It is apparently transmitted to the infant from the mother during passage through the birth canal. It appears from the fifth to the tenth day of life, and its course, while self-limited, may extend over a period of many months. Diagnosis can only be established by means of examination of Giemsa-stained preparations of the conjunctival secretions. Cultures are either sterile or show only the usual nonpathogenic conjunctival organisms. In the absence of a specific therapeutic agent, treatment should be symptomatic, with the prevention of secondary infection.

Bacteriologic studies should be made a part of the routine in examining every case of ophthalmia neonatorum, however mild, and each examination should include a study of the exudate and conjunctival scrapings after special staining by the Giemsa method.

#### CASE REPORTS

Case 1.—S. A., a boy. Unit No. 124109, was born Jan. 8, 1937, at another hospital in the city, Credé prophylaxis being used. On January 17, the tenth day of life, the infant developed a bilateral purulent conjunctivitis, so severe that both eyes were swollen completely shut. The mother had a vaginal discharge prior to delivery, but gonococci could not be identified by smear or culture. Cultures of the eye discharge failed to reveal gonococci. Treatment with boric acid and argyrol failed to result in improvement, and the infant was referred to this hospital for treatment.

Examination on January 31 showed both eyes to be swollen completely shut, with marked edema and redness. There was a bilateral beefy red papillary conjunctivitis, and the bulbar conjunctiva of the right eye was injected. The corneas were normal. The discharge was quite profuse, but thicker from the right eye than the left. Four successive cultures and smears failed to reveal the presence of gonococci. Four cultures on Bradford's medium failed to show any growth. Smears by Gram's method showed no organisms. Giemsa stained preparations showed the presence of a moderate number of cytoplasmic inclusions and free elementary bodies in both eyes.

Treatment was begun with cold compresses, boric acid irrigations and mercurochrome. The acute phase subsided in four days, but the beefy red appearance of the conjunctiva persisted for several weeks. This child has been examined at monthly intervals. The secretions have gradually diminished and, at the last examination, there was only a moderate conjunctivitis, without noticeable discharge. Inclusions could be demonstrated for four months, but at the last examination none were found.

Case 2.—C. A. B., a girl, Unit No. 123724, one of female twins, was born in this hospital Jan. 19, 1937. Credé prophylaxis being employed. A mild conjunctivitis was noted on January 28, involving only the left eye. There was a small amount of purulent exudate present. Cultures and smears were made which showed the presence of nonhemolytic staphylococci and diphtheroids. Giemsa staining showed a large number of typical cytoplasmic inclusions.

The infant was seen in the pediatric out-patient department on February 11, at which time the right eye had become involved in a similar manner. Both eyes

were sealed shut with a gummy secretion. The conjunctivae were moderately reddened. Bacteriologic studies again showed diphtheroids and nonhemolytic staphylococci, while cytoplasmic inclusions were numerous in the secretions from both eyes.

Treatment was begun with boric acid and mercurochrome. Cultures on three subsequent occasions were sterile, while inclusion bodies continued to be numerous. At the last examination, the conjunctivitis had dwindled to a small collection of secretion at the inner canthi, and a mild redness of the conjunctivae. Inclusions were not found at the last examination five months after the onset. This infant is now developing the physical characteristics of mongolism. The twin is entirely normal and has not shown any signs of conjunctivitis.

CASE 3.—P. E., a girl, Unit No. 125653, was born at home on March 10, 1937, Credé prophylaxis being used. On March 18 there developed a profuse purulent discharge from the right eye. The left eye became involved the following day. The lids were red and edematous, and the palpebral fissures crusted and closed. The conjunctivae were beefy red. The corneas were normal. The child was referred to the hospital for diagnosis and treatment.

The infant's Wassermann and Kahn tests were negative.

Four cultures and smears failed to show any gonococci. In each instance diphtheroids and nonhemolytic staphylococci were isolated. Inclusions were numerous in Giemsa-stained preparations of material from both eyes. Subsequent examination during the next three months showed a gradual diminution of signs under treatment. Cultures were negative, but inclusions were still present in small numbers, at the last examination on June 3.

Case 4.—C., a girl, Unit No. 125842, was born in this hospital on March 20, 1937, Credé prophylaxis being used. She was first noticed to have a conjunctivitis on March 26. The left eye was involved first, followed in two days by a similar involvement of the right eye. Examination on March 29 showed slight edema and redness of the external ocular tissues, with inflammation of the palpebral conjunctivae. A small amount of purulent discharge was present. The corneas were normal.

Two successive cultures were sterile. Smears stained by Gram's method showed no organisms. A moderate number of inclusions were demonstrated in Giemsastained preparations.

The mother had a mild vaginal discharge before delivery. Repeated cervical smears were made after a diagnosis had been established in the infant, but careful examination showed suggestive inclusions in only one smear. The cytoplasmic inclusions were not typical, but because of the large number of bacteria present, it was impossible to say whether these were true inclusions. The mother's Wassermann was negative.

This infant has not been seen since the initial examination.

CASE 5.—R. J. H., a boy, Unit No. 126239, was born in this hospital on April 1, 1937, Credé prophylaxis being used. On April 7 the left eye was noted to be swollen shut with a profuse thick yellow secretion pouring from the palpebral fissure. The right eye showed a mildly reddened conjunctiva. Cultures and smears from both eyes failed to reveal any organisms. No organisms were seen in smears stained by Gram's method, but with the Giemsa stain, a moderate number of cytoplasmic inclusions were found in material from the left eye. Treatment was begun with cold compresses to the left eye and boric acid irrigations and mercurochrome instillations applied to both eyes. The left eye subsided rather promptly and the child was sent home, using boric acid and zine sulphate solution.

The child was seen in the pediatric out-patient department on April 29, at which time there was a moderate purulent exudate from both eyes. Cultures were negative,

while inclusions were found in secretions from both eyes. When last examined on May 20, there was still a mild conjunctivitis, and inclusions could be demonstrated in small numbers

CASE 6.-J. A. B., a girl, Unit No. 126807, was born in another hospital on April 12, 1937, with Credi prophylaxis being used. The cyclids were slightly swollen and discolored at birth, which was explained as being due to a difficult delivery. On April 18 the infant developed a profuse purulent discharge from both eyes. There was no history of a vaginal discharge in the mother. The child was referred to this hospital for treatment

Examination on April 20 showed marked edema and redness of the lids of both eyes. The palpebral fissures were sealed shut. As soon as they were opened a thick cre my evudate appeared. The palpebral conjunctivae were beefy red, and the bulbar conjunctivae injected The corneas were normal.

Three cultures and smears were negative for the gonococcus. Diphtheroids and a nonhemolytic staphylococcus were isolated from the left eye. A large number of inclusions were found in preparations from both eyes.

Compresses, boric acid irrigations, and mercurochrome were used, and at the time of discharge from the hospital on May 8, all that remained was a beefy redness of the conjunctivae. Inclusions were still numerous. This case was referred by a private physician, and was not seen again.

Cisi 7.-A. M. A., a girl, Unit No. 126432, was born in this hospital on April 12, 1937. The Crede prophylaxis was used. On April 21, the tenth day of life, a purulent discharge from the left eye was noted. The lids were swollen shut. The right eye was normal except for redness of the conjunctiva. The mother gave no history of vaginal discharge and her Wassermann and Kahn tests were negative.

Examination on April 30 showed a slight purulent discharge from the right eye. with redness of the conjunctiva. The left eye was swollen shut, and a profuse creamy discharge appeared between the lid margins. There was a beefy red papillary conjunctivitis. The cornea was normal. Two cultures were negative at the end of Preparations of the conjunctival secretion stained by Gram's sevents two hours. method failed to show any organisms. Giemsa stained preparations from both eyes showed many cytoplasmic inclusions characteristic of inclusion blennorrhea.

Treatment was carried out at home, and consisted of 3 per cent boric acid irriga tions and instillation of 1 per cent mercurochrome. There was prompt relief of the Three subsequent examinations again showed negative cultures acute symptoms. with cytoplasmic inclusions demonstrated in Giemsa stained preparations in each instance. The last examination on June 6 showed only a very mild reddening of the conjunctive and a trace of exudate along the lid margins. Inclusions were still pre-ent

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# ERYTHEMA EXUDATIVUM MULTIFORME WITH OPHTHALMIA AND STOMATITIS

REPORT OF TWO CASES IN CHILDREN WITH CERTAIN OBSERVATIONS ON HISTOPATHOLOGY AND ANIMAL INOCULATION

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E RYTHEMA exudativum multiforme, as first described by von Hebra,<sup>1</sup> is characterized by an eruption (macules, papules, or vesicles) of the face, neck, and extensor surfaces of the hands, forearms and legs. Von Hebra emphasized the absence of constitutional symptoms. More recently, dermatologists<sup>2-8</sup> have recognized a rare form of the disease which involves, in addition, lesions of the mucous membranes (which may precede those of the skin) and manifestations of intoxication. The disease often recurs. Ormsby<sup>8</sup> states that "in some cases the symptoms are limited to the mucous membranes only, in certain recurrences." The etiology is still obscure. Stevens and Johnson,<sup>9</sup> in 1922, reported two cases of this rare condition, which stimulated others to report similar cases.<sup>10-12</sup>

It is the purpose of the present paper to present two cases of the rare form<sup>9</sup> of erythema exudativum multiforme in children, one of which was recurrent, together with certain observations on the histopathology and the effects following animal inoculation of vesicular fluid and of blood derived from an active case.

Case 1.\*—A. L., No. 84231, a Jewish boy, aged twelve years, was admitted to the hospital Dec. 30, 1933, with an exanthem, stomatitis, ophthalmia, fever, and generalized malaise that had developed during the preceding twenty-four hours.

Family History.—The parents and two siblings were well.

Past History.—The general health of the patient had been good except for recurring attacks of rhinitis each winter. His development during infancy was normal; later he acquired the Fröhlich type of adiposity. He had measles at two years, pertussis and chickenpox at four years, and was vaccinated against smallpox at five years.

Present History.—The patient was in good health until nine days before admission to the hospital. At that time a localized swelling confined to the left side of his face appeared; it was diagnosed as parotitis. During the next three days this had largely regressed. The second day before admission marked the onset of a sore throat which rapidly became acute, with malaise and fever. He refused all nourishment the day before admission. On the development of ophthalmia, he was brought to the hospital.

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<sup>\*</sup>We acknowledge the assistance of Dr. A. R. McFarland, who diagnosed this case.



Fig. 1— $C_{183}$  1 A L box aged twelve years. Photographs taken at time of second admission a, showing involvement of nucous membranes b, and c, showing multiform unilocalar umbilicated vesicular lesions some of which have a hemorrhagic periphery

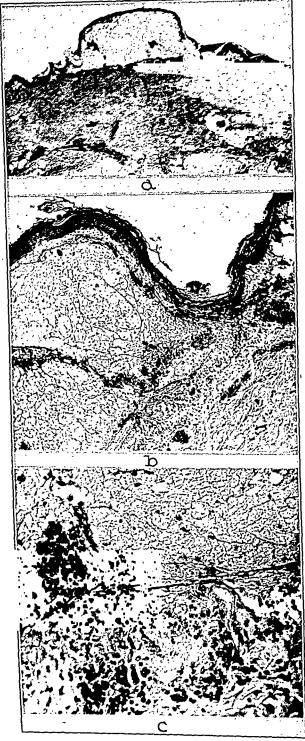


Fig. 2.—Case 1. A. L., boy aged twelve years produced for biopsy; a, showing general gross esion (X6.5); b, section through edge of lesion showing and accumulation of vesicular fluid (X60); c, higher power (X220) showing separation of overlying layers from the stratum germinativum.

Physical Examination on Admission.—Temperature 39.7° C., pulse rate, 144; respiration, 32. The patient was an acutely ill Jewish boy with the Fröhlich type of obesity. The skin was warm; no eruption was evident. Marked infection of the conjunctivae was accompanied by a moderate amount of purulent discharge. The nose and eardrums were normal. The lips were swollen, crusted, and cracked. Of the numerous bullous lesions on the soft palate and buccal mucosa, many were unbroken, whereas several had ulcerated. The tongue was coated. Both tonsils were of moderate size and red, and on the uvular surface of the left tonsil a white patch was seen. The left parotid gland was slightly swollen. There was also moderate swelling and tenderness at each angle of the jaw and in the submental region. The heart and lungs were normal. The abdomen was obese; no organs were palpable. The genitals were infantile. No abnormal reflexes were elicited.

Laboratory Findings.—Blood studies on admission revealed red blood cells, 6,600,000; hemoglobin, 15.5 gm.; white blood cells, 17,800—polymorphonuclears, 74 per cent, basophiles, 1 per cent, lymphocytes, 22 per cent; monocytes, 3 per cent. Five days after admission white blood cells numbered 6,200; polymorphonuclears, 47 per cent; basophiles, 1 per cent; eosinophiles, 6 per cent; lymphocytes, 39 per cent; and monocytes, 7 per cent.

The blood Wassermann test was negative.

Blood cultures on the first and fifth days following admission were negative.

Urine on admission showed 1+ albumin. Other analyses were negative.

Nose and throat cultures were negative for Corynebacterium diphthcriae. Thirty per cent of the colonies in the throat culture were Streptococcus hemolyticus.

A smear from mouth lesions showed no fusiform bacilli or spirochetes, and cultures from purulent conjunctival discharge showed that the predominating organism was Staphylococcus aureus.

Schick, Dick, and Mantoux (0.1 mg.) tests were negative.

Course.—On the sixth day after the onset of the illness, several small, round, vesicular lesions were noted on the chest and extremities. These enlarged and, together with the new ones which appeared during the next few days, became bluish in color with a surrounding area of erythema (1 to 4 cm. in diameter). A profuse purulent exudate drained from both eyes. Blanching with adrenaline demonstrated that the infection was limited to the conjunctivae; the corneae remained clear. Treatment of the eyes consisted in the conjunctival instillation of a solution of metaphen (1:2,500) every three hours, preceded and followed by boric acid irrigations. Definite improvement was noted six days after treatment was started. Over a period of nine days the temperature gradually subsided from 40.5° C. to normal. The skin lesions faded with slight pustulation and no scarring.

The patient was entirely well for six months (until June 27, 1934) when, following an afternoon of swimming, he again complained of sore throat. This continued to be slight for several days. On July 3 he complained of malaise. A "small lesion" was seen by a local physician on one tonsil that day. Others appeared in the mouth during the night and his temperature rose. He was admitted to the hospital on July 4.

Physical Examination on Admission.—Temperature was 39.4° C.; pulse rate, 144; respiration, 35; blood pressure, 124/90. The patient again appeared neutely ill and uncomfortable. The conjunctivae were moderately injected, and a small amount of purulent exudate was present. Both palpebral and bulbar conjunctivae were involved, especially at the periphery. The lips were moderately swollen, and there was a large bleb at the left corner of the mouth. The entire buccal mucosa, tongue, palate, and pharynx were covered by a thick, white coat through which no vesicles or ulcers could be seen. Swallowing was painful. The anterior and posterior cervical lymph nodes were tender and moderately swollen, with some swelling of the surrounding soft tissues. The skin was clear.

Laboratory Findings.—Blood studies on admission showed red blood cells, 4,870,000; hemoglobin, 15 gm.; white blood cells, 12,450—polymorphonuclears, 85 per cent; lymphocytes, 11 per cent; and monocytes, 4 per cent. Seven days after admission a count showed red blood cells, 4,800,000; hemoglobin, 12.5 gm.; white blood cells, 10,800; polymorphonuclears, 64 per cent, eosinophiles, 1 per cent, lymphocytes, 28 per cent; and monocytes, 7 per cent.

The blood Wassermann test was negative.

Aerobic blood culture on the fourth day following admission showed no growth, and an anaerobic culture on the seventh day showed no growth.

The urine, on admission, contained albumin. Other analyses were negative.

Nose and throat cultures were negative for Corynebacterium diphtheriae and hemolytic streptococci.

Smear from mouth lesions was negative for Vincent's organisms.

Vesicle cultures on third day showed no growth. On fourth day they showed a few colonies of Staphylococcus aureus.

Schick, Dick (also with heat-stabile or endogenous streptococcic toxin), and Mantoux skin tests were negative.

Other laboratory work, hearing on adiposity, is omitted.

Biopsy Examination.—A recently formed vesicular lesion was removed, placed in Zenker's acetic 5 per cent fixative for twenty-four hours, and then stained with hematoxylin cosin and Giemsa stains.

Histologic examination showed pigmented skin which was hyperplastic around the periphery of the lesion. The overlying layers of the epidermis were compressed and elevated from the underlying stratum germinativum by an accumulation of coagulated fluid in which strands of fibrin and an occasional polymorphonuclear cell and lymphocytes were present. The entire epithelium was intact with no evidence of necrosis and ulceration. The blood vessels of the corium showed evidence of dilatation with perivascular cellular infiltration and proliferation. Scattered throughout the corium were occasional mononuclear and plasma cells. No multinucleated cells were seen. No inclusion bodies suggestive of virus action were present.

Course.—On the day of admission (July 4) or the second day of fever, the patient began to complain of difficulty in urination, and at that time several blebs were noted on his penis. Later that day vesicular lesions appeared on the chest. Within twenty-four hours, the whole body was covered by unilocular, vesicular lesions 0.5 cm. to 1 cm. in diameter. Some were surrounded by small areas of erythema. Two days later they were hemorrhagic, and the zones of hemorrhage enlarged. Cultures from the vesicles at this stage showed no growth. One lesion removed for biopsy at this time is described above. Meanwhile, the purulent discharge from the eyes had become very profuse and necessitated hourly irrigations. The corneae did not become involved. Atropine ointment was used. On July 9 the temperature was normal (six days after the onset of fever). The lesions dried and desquamated without scarring.

After the patient had recovered, a search was made for foci of infection. X-ray films of the sinuses, teeth, and chest were negative. The tonsils were small, but since these episodes were preceded by sore throats, tonsillectomy and adenoidectomy were done two weeks after recovery. No histopathologic examination was made of the tonsils.

The patient had an acute attack of appendicitis with appendectomy and uneventful recovery during October, 1935. Histopathologic examination of the appendix revealed an acute inflammatory process as evidenced by closure of the lumen and infiltration of all layers with polymorphonuclear cells. A fibrinous exudate was present on the serosa.

He was well until June 3, 1936. On that day rhinitis and slight cough began (the first since July, 1934). On June 10 his throat became sore and lesions began to appear in his mouth similar to those he had had before. He was brought to the out patient department for examination and treatment. His mouth and throat showed many resicular lesions of varying size, some already broken. He had no fever, malaise, skin lesions, or conjunctivitis. He was given directions for sodium perborate mouth washes, nonirritating foods and aspirin, 0.65 gm. t.i.d. The mouth lesions persisted for five days, then cleared rapidly without the appearance of other signs or symptoms. No laboratory work was done.

CASE 2.\*—V. R. No 114042, an Italian girl, aged fifteen years, was admitted to the hospital April 9, 1936, with an exanthem, stomatitis, ophthalmia, fever, and malaise of eight days' duration.

Family History .- The parents and siblings were well.

Past History.—Her health had always been good. She had had only the usual childhood infections. Until tonsillectomy at ten years, she had numerous sore throats, but none since. There was no history of allergy or of rheumatic fever in the patient or her family.

Present History.—The patient was in good health until eight days before admission to the hospital (April 1), when she developed blisters on her lips. The blisters later appeared in her mouth and throat. Fever and a moderate diarrhea began at this time. On April 6 she developed red, flat lesions on her hands, forearms, and legs. These increased in number during three days and developed vesicles. They itched slightly. She had no chills, nor vomiting. No medication was given at home.

Physical Examination -On admission the temperature was 38.6° C.; pulse rate. 88; respiration, 20; and blood pressure, 110/60. The patient was a well developed girl of fifteen years, acutely ill and drowsy. Large, rosy cruptions were present over the forearms and hands. Smaller ones were present on both legs and ankles, topped with vesicles. The larger lesions were umbilicated, the vesicles forming an irregular circinated border, the fluid clear and amber. There was no hemorrhage, and the erythema blanched on pressure. The ears and nose were normal. The conjunctival were injected. A small amount of purulent evudate was present. There was slight photophobia. The corneae were clear, and the pupils reacted well. The lips were swollen; bleeding, shallow, necrotic irregular ulcers covered the entire buccal mucous membrane. The hard palate was covered with small vesicles, and the tongue showed eroded ulcers on the margins The uvula was edematous. The tonsils were out. The thyroid was not enlarged. Small, firm, nontender submaxillary and posterior cervical nodes were palpable. No pathologic changes were found in the chest. The pulse was from 90 to 110 per minute. The abdomen was normal Pelvic and rectal examinations were negative. The extremities which showed sluggish reflexes were otherwise normal.

Laboratory Findings—Blood studies on admission showed red blood cells, 1,990,000; hemoglobin, 14 gm.; white blood cells, 9,800—polymorphonuclears, 70 per cent, co-inophiles, 1 per cent, bisophiles, 1 per cent, lymphocytes, 23 per cent, and monocytes, 3 per cent.

Five days after admission the results of a study were white blood cells 10,350—polymorphonuclears, 80 per cent, lymphocytes, 20 per cent.

The blood Wassermann was negative.

Sheep cell agglutination test (April 10) resulted in no agglutination.

The urine was entirely normal on two examinations.

<sup>\*</sup>We are indebted to Dr. W. S. McCann, Professor of Medicine, for his permission to include Case 2, and to Dr. H. C. Shaw, who established the diagnosis and outlined the treatment of this case.

The electrocardiographic findings were as follows: Rate, 80; P-R interval, 0.29 sec.; QRS interval, 0.07 sec.; QRS slurred in Leads I and III; S-T elevated in Leads I and II; T<sub>2</sub>, low. Ventricular extrasystoles were noted.

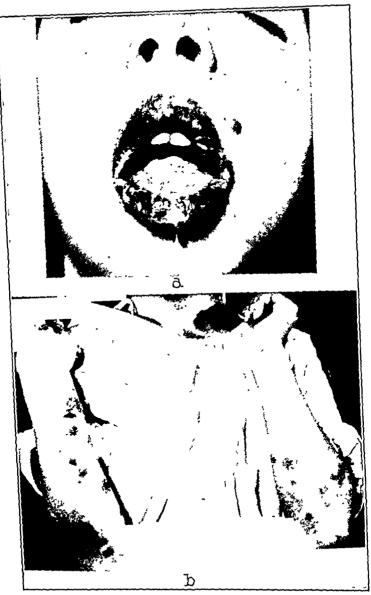


Fig. 3.—Case 2. V. R., girl aged fifteen years: a, showing involvement of mucous membranes; b, showing irregular vesicular lesions.

Course.—The patient's temperature ranged from 39 to 38° C, during the first four days after admission (ninth to thirteenth days of illness) and was then normal. Sedium perborate mouth washes were given every three hours, and boric acid eye irrigations were given every two hours during the day. Sodium salicylate, 4 gm., and

## A STUDY OF THE PROPHYLACTIC EFFECTS OF PERTUSSIS VACCINE

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IN APRIL, 1934, fifty children at the Summit County Children's Home, who had never had pertussis, were given pertussis vaccine (Sauer). Fifty other children of comparative age in the same institution, who also had never had pertussis, were used as controls. Each child vaccinated received the complete immunization as recommended by Dr. L. Sauer. The initial dose consisted of 1 c.c. of the vaccine injected hypodermically in each arm; seven days later,  $1\frac{1}{2}$  c.c. were injected in each arm; seven days after the second dose,  $1\frac{1}{2}$  c.c. were injected in each arm, making a total dosage given of 8 c.c. within a period of two weeks. No unusual local or systemic reactions followed the injections.

The Summit County Children's Home receives the orphans and wards from the Courts of Summit County. The children are usually kept over a long period of time which gives the opportunity to follow and study them. They attend the public schools of the city and thus are exposed to all of the contagious diseases prevalent in the community.

In April, 1936, two years after the pertussis vaccine had been given an epidemic of pertussis broke out in one of the departments in which 29 children between the ages of three and seven years were living. This department was immediately isolated and no child was permitted to leave except to exercise on the playground when the other children of the Home were in school or at their meals.

The 29 children in the department under observation were classified into three groups. The first was made up of 12 children who had never had pertussis, and had not received pertussis vaccine; the second group consisted of 9 children who had received complete pertussis immunization two years previously; the third comprised 8 children in the department who had had pertussis. Five of the 8 cases (Nos. 22-25 and 29) had pertussis at some previous date in the Children's Home. Cases 26, 27, and 28 had definite attacks of pertussis before entering the institution.

It is of interest to note that the disease remained limited to this department and no other case developed in the institution. During the entire period of observation, which lasted over seven weeks, all the children in the quarantined department played together; had their meals in the same refectory and slept in the same dormitory. This provided repeated, severe multiple daily exposures for all of the children and should be a

far greater test of the efficacy of the vaccine than could be obtained from a series of cases observed in individual families where mild, infrequent exposures normally would be the rule.

The children under observation were supervised by nurses; two being on duty during the day and one at night. The nurses neither knew who had been given pertussis vaccine nor why the experiment was being conducted, thus eliminating all personal bias from the study.

During the first week of the observation the nurses, at the end of the day, gave their impression of each individual's coughing. If coughing had occurred they recorded it as hard or light. After one week it was realized that no definite information could be obtained with this method of evaluation. The nurses were then requested to chart with a vertical line each paroxysm. The length of the line denoted the severity of the paroxysm and we recognized four gradations from mild to severe as can be seen on the accompanying charts. The letter W was used when a definite inspiratory whoop occurred. The nurses carried the chart with them wherever the children went, out on the playground, in the refectory and into the dormitory for naps or for the night's rest. No medication was administered to the children during the entire course of the disease except codeine, which was given very sparingly and only to the more severe cases, especially at night.

A glance at the accompanying chart shows better than anyone can narrate the course and severity of the various groups to the common infection, pertussis. No detailed study seems necessary and will not be attempted in reviewing the results, for the answer is so obvious.

Group 1, those cases who never had pertussis nor received the prophylactic vaccine, all ran a typical course. Ten of the 12 cases had a paroxysmal cough throughout the entire seven weeks of the observation, while two of the cases (Nos. 6 and 8) were content with but five weeks' coughing. On the whole the cases were but moderately severe.

Group 2, those children who had the pertussis vaccine two years previously, had a comparatively easy time. Three weeks was the average length of the attack for 6 of the 9 cases. One (No. 19), coughed but one week; No. 20 coughed but one day and No. 21 was without a coughing paroxysm during the entire period of observation. On the whole as can be seen from the chart, the paroxysms were notably less in number and severity as compared with Group 1.

All of Group 3, those children who had a positive history of pertussis previous to the study, had coughing paroxysms. Six coughed for periods averaging about three weeks, while eases Nos. 24 and 28 coughed but one week. The paroxysms were neither so frequent nor severe as Group 1, but it is extremely interesting to note that of this group not one case escaped having a mild form of the disease, and certainly as a group, coughed as much as the children protected by the vaccine.

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Chart 1.-Cont'd.

A study of the chart reveals the fact that the children not protected by the vaccine or a former attack of pertussis, had what we recognize as a typical attack and course of pertussis. The group immunized by the vaccine, had an extremely mild form of the disease and in one instance, was seemingly completely protected from the disease. The third group who had pertussis previously, developed a mild secondary attack of the disease in all instances. This is in direct variance to the usually accepted idea that an attack of pertussis confers a lasting immunity in the vast majority of cases.

No complications were encountered in any of the cases during the seven weeks of the study. Unfortunately, no laboratory work such as cough plate cultures or blood counts, could be attempted because of the lack of facilities, time, and finances. This would have confirmed some points that may be in doubt. It is hoped that this will be attempted in the future, should the occasion arise for a similar study.

#### CONCLUSIONS

- 1. Pertussis vaccine (Sauer) confers a relative immunity within a period of two years from the time of administration and the results would seem to justify the continuance of its use.
- 2. Immunity resulting from the use of pertussis vaccine (Sauer) is as effective as a previous attack of the disease in conferring immunity upon children.
- 3. An attack of pertussis does not confer complete immunity from a mild recurrence of the disease.

### HODGKIN'S DISEASE WITH TERMINAL EOSINOPHILIA OCCURRING IN A NEGRO CHILD WITH SICKLEMIA

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THE occurrence of Hodgkin's disease in a colored patient belonging to a family displaying the sickling tendency may be but a simple coincidence. Nevertheless, such a combination is so unusual that it warrants the following case report. In the comprehensive reviews of Hodgkin's disease by Symmers (1924), Simonds (1926), and Wallhauser (1933), no mention is made of any instance in which this particular combination occurred. Furthermore, the presence of true blood eosinophilia in Hodgkin's disease is now regarded as a rarity, even though tissue eosinophilia is very frequently encountered. Sears, in 1932, was able to collect from the literature only thirteen cases of Hodgkin's disease with peripheral eosinophilia, the only cases not included in his tabulation being the earlier reports by Glanzmann (1915) and by Steiger (1915), and those recently presented by Holzknecht (1932) and by Coburn and Pritchard (1934). Moreover, the present case embodies certain histologic features which require a new interpretation, particularly with reference to the histogenesis of the mononuclear and multinuclear giant cells regarded as pathognomonic of the disease. The interpretation herein offered is suggested as a possible basis for reconsideration of Hodgkin's disease as to its proper nosologic position.

#### REPORT OF CASE

T. P., a fourteen-year-old negro male, was admitted to Provident Hospital, Chicago, July 13, 1935, with complaints of (1) shortness of breath, (2) 20ugh, and (3) swelling in left side of the neck. The onset of the present illness was thought to have begun when the child fell about 10 or 15 feet from an iron pole he was attempting to climb some two months previous to his hospital admission. The patient landed face downward but did not become unconscious. However, he did vomit fresh blood shortly afterward. A "lump" was present in the right chest wall for about one week following the accident following which it disappeared spontaneously. Three weeks later, however, a large swelling making its appearance at the base of the left side of the neck brought the patient to the out-patient clinic of the hospital.

Past History.—The child's birth, in Provident Hospital, April 24, 1921, was normal; he was breast fed for nine months, sat up at six months, walked at ten months, and talked at eighteen months, though never plainly. Previous illnesses were an attack of pneumonia at ten months, and measles followed by chickenpox at four years. The interim history was irrelevant, the several clinic visits up to the age of thirteen being chiefly for dental caries and behavior problems.

Out-patient examination (Chest Clinic) revealed "dullness in the midline from the clavicle to the diaphragm, extending laterally in both directions well into the

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lung fields; the breath sounds were very distant." Fluoroscopic examination at the time confirmed these findings and a clinical diagnosis of "mediastinal tumor, probably lymphosarcoma" was made. Three days later a roentgenogram (Fig. 1) enabled the roentgenologist (Dr. B. W. Anthony) to make the following report: (1) Massive mediastinal tumor, in all probability a malignant lymphoma; (2) aorta not visualized, likewise the heart not outlined; (3) low grade but frank left hydrothorax and thickening of the left pleura.

Family History.—Father died of epidemic meningitis; mother "thinks she has a tumor of the uterus." Four siblings were born at full term; there were no miscarriages. Patient's maternal aunt and great-grandfather died of tuberculosis.

Physical Examination.—The following positive findings were obtained upon admission: (1) Dyspnea and marked orthopnea; (2) dry brassy cough; (3) occasional choking sensation and difficulty in swallowing; (4) soft bilateral swelling of the neck anteriorly; (5) dullness over the entire thorax bounded by the clavicle above, the diaphragm below, and the midelavicular lines on both sides; (6) markedly

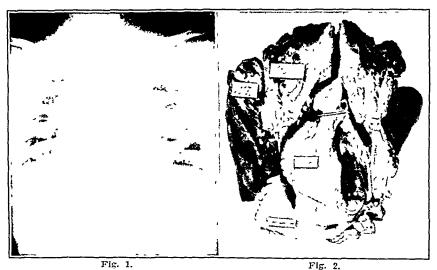


Fig. 1.—Roentgenogram of the chest (July 16, 1935).

Fig. 2.—Photograph of the mediastinal mass removed at autopsy, showing its relation to the heart and the lungs (Aug. 13, 1935).

diminished breath sounds over the area of dullness; (7) indistinct apical heart beat; and (8) increased anteroposterior diameter of the chest. Temperature was 100.2° F., pulse rate, 65; and respiration, 35 per minute; blood pressure registered 140/78.

Laboratory studies showed the urine to be negative and the sputum negative for tubercle bacilli. Routine blood counts are tabulated in Table I. Coagulation time

TABLE I
SUMMARY OF BLOOD COUNTS

DATE	E.B C.	HB Cc (SAHLI)	W.B.C.	r	L	М	E	В
7/23/35	4.05	80	7,800	65	28	2	2	0
7/28/35	4.50	75	14,300	-	_	_	-	-
8/ 6/35	5.10	55	23,600	-	-	-	40	_
S/ 9/35	4.80	60	26,000	43	3	5	47	2

was 3.5 minutes; bleeding time, 4 minutes. Blood Wassermann and Kahn tests were negative. The Beck and Hertz method (1935), as well as the standard coverslip method, for testing of the sickling tendency of the red blood corpuscles was applied to this patient's erythrocytes, and both were markedly positive in twelve hours (Fig. 3). The same methods of study were then applied to the red blood cells of the mother, which were found also to be 50 per cent positive in twenty-four hours. Other members of the family were not tested.

Biopsy of a lymph gland from the right axilla was made on July 27, 1935, with the following report: "The microscopic study reveals no characteristic pathologic picture. There is a marked increase of eosinophiles scattered throughout the gland. There is also an increase of polymorphonuclear leucocytes above the normal. The red blood corpuscles show sickling in the blood vessels." (Fig. 4.)

Because of increasing dyspnea and edema of both legs, a second roentgenographic examination was made (Aug. 6, 1935) and revealed "moderate increase in size of

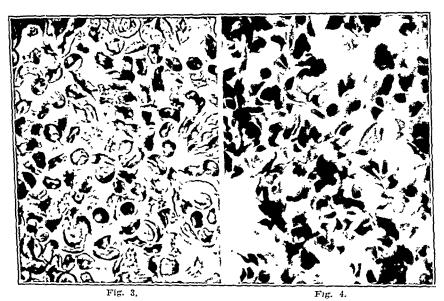


Fig. 3.—Photomicrograph of the patient's erythrocytes at twelve hours (standard cover-slip method) (×1500).

Fig. 1.—Photomicrograph of blood clot within a capillary of the lymph node removed by blopsy, showing the presence of numerous sickle cells (×1500).

the mediastinal tumor mass; increase in the pleural effusion in the right chest cavity." The day following this report a thoracentesis of the left pleural cavity was done and 450 c.c. of dark straw-colored thick fluid removed. The fluid clotted so very quickly after removal that the specific gravity could not be determined. Microscopic examination revealed (1) many erythrocytes showing macrocytosis and polychromatophilia, nucleated red cells, and cells incompletely sickled; (2) the leucocytes consisting of many large cells with a single large round nucleus and a pale agranular cytoplasm, and many granular forms with bilobed nuclei resembling cosinophiles. The cholesterol content of this fluid was reported to be 615 mg. per cent, and the culture negative. Another roentgenogram made immediately after thoracentesis disclosed no additional pathology except for a diminished amount of fluid in the left pleural cavity. Because of the rapidly progressing weakness of the patient, no further investigations were attempted. Death ensued on Aug. 12, 1935.

Clinical Course .- On admission, the patient was found to be well nourished, very alert, little disturbed by his dyspnea, orthopnea, or brassy cough. cachexia and anemia commonly reported in cases of this type were at no time seen in this patient. Except for a slight epistaxis and a somewhat increasing orthopnea, the patient's condition was unchanged until the twelfth day after admission, at which time he first complained of pain in the ankles, and examination of the latter revealed a pitting edema not previously noted. The dyspnea and orthopnea increased to the extent that the patient was unable to obtain any relief except by sitting in a wheel chair and bending well forward. He could not be induced to leave the chair for the bed. The swelling of the ankles spread so rapidly upward involving the legs and abdomen that within three days he was unable to move his lower extremities, and all sensation was abolished below the level of the hip. The thoracentesis above referred to was done four days before the patient died, at which time such alarming symptoms as incontinence, cyanosis, and anasarca were already present. Removal of the fluid from his left pleural cavity caused a temporary relief of symptoms for about twenty-four hours, following which cyanosis and dyspnea reappeared even more markedly than before. Until the seventh day before his death, when it fell to 98° F., where it remained until the end, his temperature during the entire stay in the hospital ranged between 99° and 100° F., except for a rise on two occasions to 101° F. The pulse rate was from 60 to 65 per minute on admission, but increased soon afterward to 120 to 140 per minute. Before death it fluctuated between 80 and 180 per minute. One deep x-ray therapy (300 r.) over the upper mediastinum through the back was given on the day before his death.

Autopsy Protocol.—The postmortem examination, made by Dr. M. M. Shaw thirty hours after death, resulted in the following anatomic diagnoses: (1) Mediastinal lymphogranulomatosis Hodgkini with spread to the lungs and the pericardium; (2) bilateral hydrothorax; (3) parenchymatous degeneration of the myocardium;

- (4) parenchymatous degeneration of the kidneys; (5) induration of the spleen;
- (6) marked anasarca, especially of the upper extremities, the face and the neck;
- (7) sickle-cell anemia.

The more important gross and microscopic findings are summarized as follows:

Picural Cavities.—The removal of the sternum was difficult because of its adherence to the underlying mediastinal mass. Both pleural surfaces were smooth and the cavities contained about 300 to 350 c.c. of a clear, straw-colored fluid. A large mediastinal mass extended laterally into both pleural cavities. The lungs were collapsed.

Pericardial Cavity.—Though compressed, the pericardial cavity contained a straw-colored fluid somewhat in excess of the normal. The inner surface of the sac was smooth and glistening, but the external surface was studded with numerous nodules varying in size from 0.8 to 3.0 cm. in diameter. The masses, gray white in color, cut with some increase in resistance, revealing a white firm surface with white fibrous bands crossing the substance.

Trachca, Bronchi, and Esophagus.—These structures were surrounded and partially compressed by the mediastinal mass together with the adjacent enlarged lymph nodes. The compression did not cause obstruction. The mucosa of the trachea and bronchi was pale and covered with an increased amount of white mucoid material. The esophagus was compressed and pushed to the right of the midline.

Thyroid and Thymus.—The thyroid, weighing 25 gm., was smooth, lobulated, pale tan in color, and the surface, upon cutting, was glistening. The thymus had undergone physiologic atrophy.

The Heart and Vessels.—The base of the heart was compressed by the mediastinal mass. Its transverse diameter was 8.5 and the longitudinal 10.5 cm. The wall of

the left ventricle was 12 mm. in thickness; the right, 3 mm. The myocardium was pale gray brown and of good consistency. The endocardium was smooth, with no significant valvular changes. The ascending portion and the arch, together with the first part of the descending aorta, as well as the pulmonary arteries, were surrounded by the mass and compressed by it. The aorta was thin-walled, the intima smooth, with no evidence of invasion by the mass.

Mediastinal Mass.—The mediastinal mass, measuring 15 by 15 by 9 cm. in its greatest dimensions, pale gray to pinkish gray in color, was irregular in shape, nodular and very firm. The central portion, more dense than the periphery, was composed of a mass of densely adherent glands indistinguishable in the midportion, but revealing individual lymph nodes at the periphery, measuring 1 to 7 cm. in the greatest diameter. No areas of necrosis, even in the interior of the mass, were present (Fig. 2).

Lungs and Tracheobronchial Nodes.—The lungs were compressed by the fluid in the pleural cavities. Because of the deposits of black pigment, the pleura was blackish gray in color, and was studded with firm, whitish masses similar in consistency and structure to the mediastinal mass. The mucosa of the bronchi was pale and was covered by an excessive amount of mucoid material. The tracheobronchial nodes, much enlarged, formed a part of the tumor mass. The normal parenchyma was replaced by the firm, dense, gray tissue.

Liver, Gallbladder, and Spleen.—The liver, weighing 1,400 gm., was increased in consistency. The capsule was smooth and grayish in color, with rounded edges, and its cut surface revealed distinct lobular markings with a yellowish zone about the central veins. The gallbladder was normal. The spleen, weighing 165 gm., was firm with rounded edges. It cut with some resistance, disclosing a dark purple parenchyma in which the trabeculae themselves were distinct but their follicles indistinct.

The organs of the urogenital system, together with the adrenals and the entire gastrointestinal tract were normal.

Lymph Nodes.—The mediastinal, the tracheobronchial, and the cervical nodes were all enlarged and firm, revealing on cutting the replacement of the parenchyma by the dense hyperplastic gray tumor tissue.

Histology.—The histologic sections of the tumor mass at various locations revealed a specific granuloma composed of epithelioid cells and epithelioid giant cells of the Sternberg-Reed type with varying amounts of fibrous tissue reaction. There were many small round cells with a few plasma cells and a tremendous infiltration of cosinophiles. In areas the cosinophiles were so compact as to give a distinct redness to the section even on gross inspection. Some of the sections showed a granular necrosis with obliteration of the cellular structure and details. This portion took an irregular pale stain with eosin. Some of the lymph glands contained small foci of lymphoid tissue near the periphery, but for the most part were replaced by the tumor tissue. The capsule of the gland was greatly thickened.

The sections of the masses in the lung and in the parietal pericardium were similar in structure, with the fibrous tissue, the epithelioid cells, and the Sternberg-Reed giant cells. In all sections of the granuloma cosinophiles were densely collected.

The small blood vessels and capillaries in these sections were filled with clongated, pointed or sickled crythrocytes.

#### COMMENT

The association of peripheral cosinophilia with Hodgkin's disease, though an old observation, is so unusual that brief comment may not be amiss. From the time Goldmann (1892) first observed, and Kanter

(1894) and Ziegler (1911) emphasized, an eosinophilic infiltration of lymph nodes in Hodgkin's disease, the impression has been widespread that blood eosinophilia is also characteristic of the disease. Fabian (1910) stated that slight eosinophilia (4 to 6 per cent) in the circulating blood occurs in about one-fourth of the cases. More accurate statistical studies, however, fail to substantiate this impression. In analyzing 108 cases of Hodgkin's disease in children Smith (1934) was led to believe that the blood picture is so relatively inconstant as to be of little diagnostic significance, a conclusion also arrived at by Corbeille (1928) after analyzing 33 cases of childhood Hodgkin's disease. Moreover, Roth and Watkins (1936) in their study of the leucocytic picture in 40 cases of Hodgkin's disease made no comment as to eosinophiles, since their cases all showed a normal eosinophilic percentage.

While blood eosinophilia is of rare occurrence in Hodgkin's disease, it is noteworthy that in the presence of progressive lymphadenopathy the increase in circulating eosinophiles is at least suggestive of the The blood picture in Hodgkin's disease, as pointed out by Bunting (1914) and others, appears to depend primarily upon the duration and stage of the disease, and thus there can be no typical or even characteristic findings either in the total leucocyte count or in the relative percentage of any single strain of blood cells. Chevallier (1931), Klima (1931) and Goia (1933) noted that eosinophiles usually increase in number only when the total leucocyte count is elevated, the cases with leucopenia ordinarily showing no deviation from a normal percentage of eosinophiles. Among the cases tabulated by Sears (1932) the lowest total leucocyte count (11,000) was that reported by Weber and Bode (1927), with 50 per cent eosinophiles (absolute number, 5,500), while the highest total count (100,000) was recorded by Stewart (1933), with eosinophiles varying from 72 to 90 per cent (absolute number 72,000 to 90,000). case here presented, the initial leucocyte picture was normal both in total and absolute counts, but the terminal picture was characterized by a distinct leucocytosis and outstanding eosinophilia. The absolute number of circulating eosinophiles during the last stage of the disease climbed to 12,000, quite in keeping with the cases reported by Bunting (1914) and by Sibley (1915). Such a remarkable blood picture is seldom encountered in any other disease, the closest resemblance being in chronic myelogenous leucemia (Stillman, 1912), in cases of familial or constitutional eosinophilia (Stewart, 1933) and in the so-called eosinophilic leucemia (Shapiro, 1919; Aubertin and Giroux, 1921). the present case all these conditions must be considered as possibilities, even though lymphogranuloma is the indisputable diagnosis as judged by the underlying pathology which is discussed below.

The histopathologic changes in the lymph node as seen in the sections prepared from biopsy material consisted mainly in the enlargement of the gland with increased reticulum fibers, the meshes of which were densely infiltrated with eosinophilic and neutrophilic granulocytes. No typical reticulum cells of the Sternberg-Reed type were seen although fibrosis was in evidence. From the histologic examination of the tissue alone the diagnosis of lymphogranuloma was, accordingly, but a presumptive one. Practically every tissue studied at autopsy, however, revealed the true Hodgkin's picture. Not only did the macroscopic findings demonstrate the typical manner in which the disease spreads, but the microscopic appearance of the tissues possessed all such classical characteristics as epithelioid cells and epithelioid giant cells of the Sternberg-Reed type, dense eosinophilic infiltration, granular necrosis, and fibrosis (Fig. 5). The terminal eosinophilia with leucocytosis in the present case constitutes a unique feature of the disease. In the absence of an increase in peripheral eosinophiles the lymph node obtained at biopsy revealed a tremendous eosinophilic infiltration of the gland. One may reasonably assume, therefore, that even in the absence of peripheral eosinophilia the presence of large number of eosinophiles in the lymph gland is, in Hodgkin's disease, quite characteristic.

Numerous authors have commented upon the relation of eosinophilic infiltration in lymphogranulomatous tissue to blood eosinophilia. noting the large numbers of eosinophilic as well as neutrophilic granulocytes in the lymph nodes Goldmann (1892) believed them to have been derived from similar cells circulating in the blood by means of an underlying mechanism assumed to be that of chemotactic stimulus. Many subsequent observers, notably Symmers (1924), have since adopted this so-called colonization theory, but the present case clearly contradicts this view inasmuch as no increase in eosinophiles occurred in the peripheral blood even while the biopsied lymph node was densely infiltrated with these cells. But later, as the disease progressed, eosinophiles did begin to appear in the blood stream in increasing numbers, until the pronounced eosinophilia marked the terminal picture. Again, the view advanced by Barron (1926) to the effect that cosinophilic infiltration of the nodes coincides with blood eosinophilia is not confirmed by the present case.

This leaves us with only one alternative theory, namely, that the involved lymph nodes, being preeminently organs of blood-formation, are endowed normally with primitive mesenchymal cells in the form of undifferentiated reticulum cells which, when acted upon by some pathologic stimulus differentiate not only into lymphocytes as naturally occurring in lymph glands, but also into the myeloid cells normally present in the bone marrow. This possibility of a local origin of granulocytes in Hodgkin's lymph nodes was first suggested by

Kidd and Turnbull (1908), who particularly noted the presence of large numbers of mononuclear eosinophile cells (eosinophilic myelocytes) and eosinophilic micromyelocytes. Similar observations have since been made by others. In the case here presented, the periphery of the lymph nodes still retained some evidence of normal lymphopoiesis, although here also eosinophilic infiltration was so great that the entire tissue in these areas had a reddish appearance on gross inspection. The microscopic picture of the lymph node in these areas was that of a veritable myeloid metaplasia. In other words, the pathologic stimulation of the lymph nodes in Hodgkin's disease results in the extramedullary myelopoiesis of the affected tissue. We may

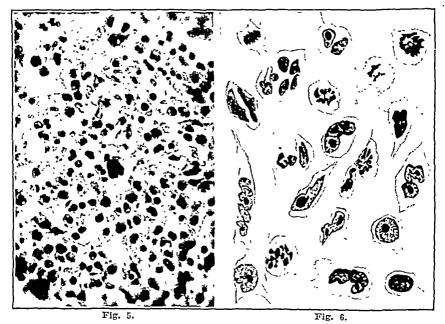


Fig. 5.—Photomicrograph of a section of the mediastinal node removed at autopsy, showing several reticulum giant cells of Sternberg-Reed type, together with dense infiltration of eosinophiles and a few neutrophiles. Some of the granulocytes are premyelocytes and myelocytes. Hematoxylin-eosin (×850).

Fig. 6.—Drawing of some of the typical reticulum giant cells (Sternberg-Reed type) found in the sections of a mediastinal mass. Nuclear configuration of some of the cells suggests mitosis. (Camera lucida, oil immersion lens, 10 ocular; Kingsley's hematologic stain.)

assume from such a viewpoint that eosinophilic infiltration of the lymph glands occurs independently of blood eosinophilia and is consequently not the result of cellular colonization from the bone marrow. Since the eosinophiles are formed in increasing numbers in the lymph glands as well as in the bone marrow, probably by both direct and indirect cell division, these cells finally escape into the blood stream, producing the unique picture presented by this case. While but a hypothesis, this interpretation alone can account for the sequence of

events which seem to have transpired in the pathogenesis of eosinophilic infiltration evidenced first by the lymph nodes and then later by the circulating blood. Irrespective, then, of the nature of the etiologic agent which activates the hemopoietic organs to develop the histopathologic picture found in the present case, it must be assumed that the fundamental pathogenesis in Hodgkin's disease is quite similar to, if not identical with, that of leucemia, an assumption advocated by Warthin (1927), Pullinger (1932), and others.

Another significant histologic feature of the lymph nodes in this case refers to the histogenesis of the reticulum giant cells, known by a great variety of synonyms. Originating from the connective tissue framework forming the bulk of the lymph sinuses in the medulla, these cells are seen to pass through progressive stages of maturation and differentiation, finally attaining enormous dimensions with multilobulated nuclei. These cells are generally regarded as the only specific cellular element which characterizes the Hodgkin's lymph nodes and have been designated as the Hodgkin cell (Potter, 1935). cytologic characteristics of the Hodgkin cell have been so carefully studied and described by Sternberg (1898), Andrewes (1902), Reed (1902), and others that their detailed description here is superfluous. It is only necessary in this connection to state that the lymph node sections demonstrated the various developmental stages by which the giant cells differentiate and that even a few of these cells presented certain nuclear characteristics strongly suggestive of mitotic division (Fig. 6).

Morphologically the well-differentiated reticulum giant cells are indistinguishable from the megakaryocytes (known also as myeloplaxes or multinuclear myeloid giant cells) of the normal bone marrow, a feature which led Medlar (1931) to regard Hodgkin's disease as a primary neoplastic disease of the bone marrow with the proliferation of the megakaryocytes as the type cells, a pleomorphic aggregation of similar cells in the involved lymph glands being merely metastatic tumor growth. A somewhat similar conception was earlier expressed by Symmers (1924) to the effect that the histogenesis of Hodgkin's disease is determined by the "discharge of mononuclear giant cells from the bone marrow and their arrest by the hyperplastic lymphoid depots in pursuit of their function as filters." Such an assumption, however, would seem unnecessary inasmuch as both mononuclear and multinuclear giant cells can be clearly demonstrated to originate and mature within the lymph nodes themselves. Moreover, such a development occurring in the lymph gland may be looked upon as added indication that myeloid metaplasia rather than metastatic tumor growth constitutes the essential histopathology of Hodgkin's disease, bringing it more in line with the category of leucemias.

Finally, the present case is unique in that the patient belonged to a sickle-cell family, as established by positive tests of his red blood cells. In the sections of the lymph glands removed at biopsy, the small vessels were filled with large clumps of blood in which were found many sickle cells. Although the patient betrayed no active symptoms of sickle-cell anemia, the coexistence of lymphogranuloma and sicklemia offers an interesting opportunity to speculate on the possibility of their having a mutual relationship. Both of these diseases, although so far as is known having nothing in common other than certain aspects of pathologic changes in the spleen, are recognized as having definite hereditary and familial tendencies. No conclusion, however, can be drawn from the observation in a single case.

#### SUMMARY AND CONCLUSIONS

- 1. A case of Hodgkin's disease with terminal eosinophilia occurring in a negro child belonging to a sickling family is reported.
- 2. Eosinophilia in the present case was a terminal phenomenon, totally absent during the early stages of the disease, although the involved lymph node removed at biopsy revealed a marked infiltration with eosinophiles. This naturally leads to a conclusion that the peripheral eosinophilia was the result rather than the cause of tissue eosinophilia. Evidence, therefore, points to the possibility that the eosinophiles infiltrating the affected node are not derived from the similar cells transported from the bone marrow by way of the blood stream, but rather these cells arise in situ as the result of myeloid metaplasia.
- 3. The multinuclear giant cells, known by numerous synonyms and regarded as absolutely unique in Hodgkin's disease, are cytologically indistinguishable from normal megakaryocytes in the bone marrow and therefore, in all probability, these cells do not constitute a distinct strain of pathologic cells but represent the differentiation of reticulum cells under the influence of some pathologic stimulation. In other words, the development of the multinuclear giant cells takes place in situ in the lymph nodes themselves and their presence is not likely to have resulted from the transportation of these cells from the bone marrow. This interpretation of the pathogenesis of the giant cells in the Hodgkin's nodes adds further evidence as regards the phenomenon of myeloid transformation of lymph glands in this disease.
- 4. On histologic grounds, then, consisting chiefly of myeloid metaplasia occurring in the lymph nodes, Hodgkin's disease resembles myelogenous leucemia, these two conditions differing in that in leucemia the blood changes are fairly constant whereas in Hodgkin's disease the peripheral blood picture is searcely altered. Thus, it is suggested that Hodgkin's disease ought to be classed among the diseases of the hemopoietic organs, particularly the lymph nodes and

the bone marrow; the characteristic changes being the disorderly multiplication of granulocytes (both eosinophilic and neutrophilic), . megakaryocytes, and lymphocytes, accompanied by a fibroblastic proliferation leading to fibrosis but in which, save for the rare instances in which an increase in circulating eosinophiles during the last stage reflects the underlying pathology of the involved tissue, the peripheral blood shows no leucemic changes.

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# SEVERE FUNCTIONAL ANEMIA IN A CHILD, RESEMBLING PERNICIOUS ANEMIA OF ADULTS

#### A CASE STUDY

JOHN M. ADAMS, AND IRVINE MCQUARRIE MINNEAPOLIS, MINN.

A GENUINE revival of interest in the anemias of infancy and child-hood has been in evidence during the past decade. This has apparently been an outgrowth of the fundamental contributions in the general field of hematology made by such investigators as Whipple, Minot, Castle, Cooley, Hart, and their coworkers. Because of the natural physiologic lability of the immature subject and the excessive demands of rapid somatic growth, the young child is peculiarly susceptible to those disturbances in nutrition or general metabolism which are thought to favor the development of certain types of anemia. Reasoning along this line, one might expect the incidence of pernicious anemia to be exceptionally high in early life, but such is not the case. In fact, this particular form of anemia is thought to be all but nonexistent before the age of ten years. However, a few authentic reports of its occurrence in older children have been recorded.

The present report deals with an unusual case of "pernicious-like" anemia in a child, who appears to have recovered completely following a course of therapy considered to be more or less specific for genuine pernicious anemia. It is thought worthy of being recorded not merely because of the rarity of this form of anemia in childhood, but more particularly because of the complete and apparently permanent disappearance of all traces of the disorder following a single course of therapy. Almost as important may be the development during convalescence of a bizarre disturbance in the general body metabolism, which suggested a transient malfunctioning of the pituitary or the adrenal gland.

#### REVIEW OF CASE

E. S., a twelve-year-old girl, was admitted to the pediatric service of the University of Minnesota Hospital on Dec. 12, 1935 with the complaint of pallor, weakness, loss of appetite, and vomiting. She had been considered to be quite well up to three weeks prior to admission, at which time she had had an acute upper respiratory infection with a cough, which still persisted. Weakness, pallor, and listlessness had become marked about ten days prior to admission, and morning vomiting had occurred repeatedly without regard to meals or activity. Slight numb-

ness and tingling of the hands were complained of on several occasions. Soreness of the tongue and buccal membranes was fairly marked. There was no history of blood loss or purpura or of poisoning of any kind. The diet could not be described with a high degree of accuracy, but the appetite had been noticeably poor and capricious for some time, according to the mother's account. Except for the frequent vomiting and this disturbance of the appetite, there were no gastrointestinal symptoms. There was no special suggestion of iron deficiency in the diet. No members of the immediate family had suffered from anemia or any similar illness. It is worthy of mention, however, that two first cousins have been treated for hemophilia in our clinic.

Physical Examination on Admission.—The patient was a well-developed but somewhat undernourished girl. Her weight was 26.5 kilograms. She was intelligent and cooperative. The temperature, pulse, and respiration were normal. The tongue was completely denuded of papillae and presented a "beefy red," slightly furrowed appearance. Pallor of the skin and mucous membranes was marked. No definite jaundice or purpuric spots were discernible, although a single small hemorrhagic area could be seen in the left conjunctival fold. The lymph nodes of the neck were slightly enlarged. The chest examination was negative except for a soft blowing systolic murmur heard over the precordium. No masses were palpable in the abdomen. The spleen, liver, and kidneys were not demonstrably enlarged. A complete neurologic examination was essentially negative.

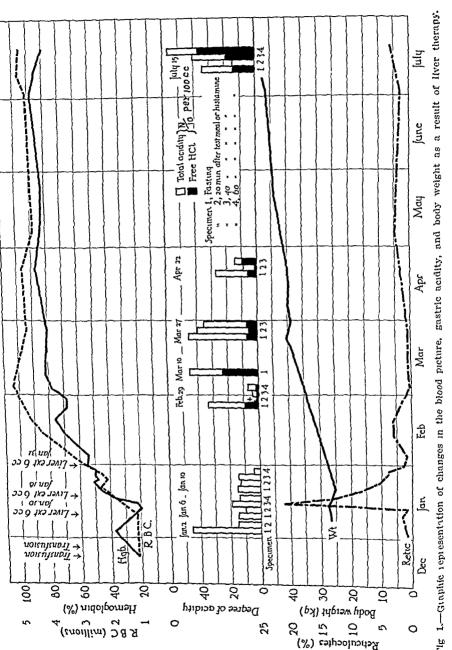
Laboratory Data on Admission.—Hemoglobin 22 per cent (Sahli), 3.5 gm. per 100 c.c. of blood (Haden); red blood cells 1,100,000 per c. mm.; white blood cells 4,900 per c. mm. with a normal differential count; platelets 190,000 per c. mm.; reticulocytes 0.3 per cent. The blood smear showed some basket cells, an occasional megakaryocyte, and immaturity in the lymphocytes. Among the polymorphonuclear cells were many band forms. The red cells showed marked anisocytosis and poikilocytosis, with a tendency to macrocytosis. Smears kindly examined for us by Dr. Hal Downey and Dr. O. P. Jones of the Division of Hematology showed "no evidence of leukemia but a severe degree of toxic anemia, the smear suggesting a 'pernicious type' of anemia with numerous 'P.A.' neutrophils." The bleeding time and clotting time were normal. The Wassermann, Kahn, tuberculin, and Shick tests were all negative. No blood or parasites could be found in the stools. The van den Bergh reaction was indirect. Urobilinogen was found to be present in the urine in traces, and the feces contained 104 mg. per day, a normal amount according to Watson.6 The sedimentation rate was 45 mm. in one hour. Urine examination was entirely negative. Serum calcium was 9.1 and phosphorus 5.1 mg. per 100 c.c. Gastric analyses showed the absence of free hydrochloric acid after test meals and after histamine administration (Fig. 1).

Clinical Course.—During the first two days after admission to the hospital, the patient ran an afebrile course without complaints other than those already referred to. On the third day, however, her temperature rose to 101° F. and remained elevated off and on during the following five weeks. The pulse rate remained exceptionally rapid during this period. She coughed occasionally, bringing up a small amount of mucopurulent material. Roentgenograms showed increased bronchial markings in the lower lung fields, suggesting early bronchiectasis. During the first three weeks no other cause for the fever was found although numerous examinations of various types were made. Blood cultures and serum agglutination tests for B. typhosis, B. paratyphosis A and B. B. melitensis, B. tularense, and B. dysenteriae, Flexner and Shiga, were all negative.

Following the preliminary diagnostic studies, the patient was given a transfusion of 500 e.c. of blood on December 23. The response to this and to a second transfusion of 525 e.c. four days later was only transitory so far as the blood picture was concerned. The hemoglobin rose from 22 to 37 per cent but again fell within a few days to 19 per cent. The patient still complained of sore tongue, especially when eating. Gastric analysis at this time (January 2) again revealed the absence of free hydrochloric acid.

Because of the pernicious-anemia-like picture, she was given liver extract (anti-pernicious-anemia factor—Lederle) intramuscularly in 6 e.e. doses on January 10 and January 18. The temperature gradually fell to normal following the first injection. As shown graphically in Fig. 1 the response to these injections was spectacular, particularly as regards the reticulocyte count. It is obvious that the mechanisms involved in hemoglobin and red blood cell regeneration were stimulated almost to their maximal capacity. Gastric analyses made on several occasions after the blood picture had returned to normal showed free hydrochloric acid, as indicated in Fig. 1.

The patient's temperature remained normal or but slightly elevated until January 29, at which time it again rose to 103.4° F. For the first time the patient complained of pain in her left thigh, and the next day showed signs of thrombophlebitis. On the following day similar symptoms and signs appeared over the right thigh also. Redness, swelling, and edema were present with acute tenderness over the saphenous vein. The abdomen was distended, and the superficial veins became somewhat prominent. During the course of this sharp febrile reaction, the reticulocyte count dropped from its maximal elevation of 21.0 per cent to 0.8 per cent. On January 31 a third dose of liver extract was administered. After approximately ten days of septic fever, the body temperature again began to decline, coincidently with subsidence of the



I'lg 1.—Graphic representation of changes in the blood picture, gastric acidity, and body weight as a result of liver therapy.

thrombophlebitis. The reticulocyte count shortly thereafter rose spontaneously to 3.0 per cent. Within a month following institution of liver therapy, the blood picture had become entirely normal and remained so thereafter. The gastrie juice continued to contain free hydrochloric acid.

To insure a complete and satisfactory convalescence, particularly in respect to the complicating thrombophlebitis, the patient was kept in the hospital for three months following subsidence of the acute infectious process. Her appetite, which had become excessive following the liver therapy, continued and the weight change was marked, representing a gain from 26 to 47 kilograms (Fig. 1). In spite of a moderate reduction in her diet, she continued to gain and complained of hunger almost continuously. In an attempt to discover the cause of her polyphagia and obesity, the carbohydrate tolerance and the basal metabolic rate were determined. The latter was found to be low on two occasions (minus 38 per cent and minus 29 per cent). Fasting blood sugar values ranged between 89 and 110 mg. per 100 c.c. The glucose tolerance test showed the following values: fasting, 89; 1 hour, 133; two hours, 122 and three hours, 106 mg. per 100 c.c. of blood. A moderate grade of acrocyanosis of the upper as well as the lower extremities gradually developed. At this time the hemoglobin ranged near the 100 per cent level, while the red blood cell count was found to be slightly above 5,000,000 on one occasion. At the same time her face became full, pudgy, and suffused. The fat was deposited chiefly over the torso, face, and neck with purplish striac formation over the abdomen and hips. X-ray pictures of the hip and the long bones showed a moderate degree of osteoporosis. These changes were sufficiently striking to suggest the adrenal cortical syndrome or Cushing's "pituitary basophilism" in an early stage. The blood pressure, however, varied between 102/58 and 108/78 only. A roentgenogram of the sella turcica was negative and no mass could be palpated in the slightly distended abdomen. She was discharged from the hospital on July 15, 1936 with this syndrome representing her only recognizable abnormality.

Since that time the patient has been examined periodically in the out-patient department. The above signs suggestive of an endocrinopathy, involving the pituitary or the adrenal cortex, have all disappeared completely. She has had no recurrence of the anemia. The blood count on June 3, 1937 was as follows: hemoglobin, 90 per cent; red blood cells, 4,710,000 per c.mm.; total white blood cells, 5,980 per c.mm.; polymorphonuclears 62 per cent; lymphocytes, 36 per cent; and monocytes, 2 per cent. No therapy has been required during the past year and there have been no symptoms or signs of illness, whatsoever. So far as can be determined at the present time, she is a normal child in every respect.

#### COMMENT

This case study is of interest primarily because it demonstrates the occurrence of a type of anemia in childhood, which resembles pernicious anemia of the adult type very closely even though proof of their identity is lacking. The fact that our patient completely recovered following specific therapy, together with lack of direct information regarding the presence or absence of the intrinsic antianemic factor in the gastric contents, makes a positive diagnosis of true pernicious anemia unjustifiable. As pointed out by Castle, Heath and, Strauss3-b the absence of free hydrochloric acid in the gastric contents does not necessarily indicate the lack of the essential intrinsic factor. Nor does return of free acid imply return of the intrinsic substance, when both have previously been demonstrated to be absent. Unfortunately special tests for the intrinsic factor could not be carried out in the present case. If any diagnostic significance can be attached to her response to specific therapy, however, it must be admitted that she probably suffered temporarily from a lack of this essential factor.

The underlying pathogenesis of the anemia in this particular case is obscure. Whether or not the vomiting was a contributing factor on the basis of loss of intrinsic substance or was merely an associated symptom dependent upon an underlying disturbance in gastric function could not be determined. Since the onset of the patient's anemia was preceded by an acute febrile illness, it seems to us that the latter may have been responsible for a transient functional disturbance of the mechanisms normally responsible for the production of both free hydrochloric acid and the intrinsic antianemic factor. The patient's striking response to parenteral administration of the latter substance and her subsequent course indicate that the deficiency was thereby corrected temporarily, after which normal function was completely restored.

Whether development of the profound disturbance in body metabolism noted following recovery from the anemia bears any relationship to the response of the hematopoietic system or not is problematic. We have been unable to find any reference to such an interrelationship in the literature. While there is some evidence which points to an intermediary effect of the anterior pituitary on hematopoiesis, insufficient data are available for a satisfactory interpretation in the present case. The clinical picture suggestive of mild "pituitary basophilism" or the "adrenal cortical syndrome" developed on what was apparently a purely functional basis, since it disappeared spontaneously and completely within less than a year.

#### SUMMARY

1. A case of severe anemia, closely resembling pernicious anemia of adults, is described as occurring in a twelve-year-old child.

- 2. Parenteral administration of liver extract (antipernicious-anemia factor) was followed by a spectacular recovery, which was apparently complete and permanent.
- 3. This was interpreted tentatively as representing a transient, purely functional disturbance in the mechanism involved in the elaboration and utilization of the intrinsic antianemic factor.
- 4. A bizarre sequela in the form of a temporary abnormality of body metabolism resembling "pituitary basophilism" or the "adrenal cortical syndrome" is likewise described.

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### FREE DIET IN CHILDREN WITH DIABETES

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THOSE with experience in the preinsulin days remember the terrible existence that diabetic children had to sustain. The extremely strict diet supplied to these unfortunate children scarcely contained anything that could appeal to the taste of children in general. In spite of all privation the result of the strict diet always became unfavorable after a very short time. With the introduction of insulin new therapeutic prospects were opened. The new remedy gave us the possibility of supplying a more liberal diet, of meeting the risks of infection with more confidence, and of overcoming the state of coma in a new way.

In my opinion, however, it would have been possible to take at an earlier date the full advantage of the introduction of insulin in therapeutics. Insulin was used in the beginning as an auxiliary to a strict-dietetic treatment, which later was regarded, and is still regarded in many quarters, as the main point. As a result, the fate of children suffering from diabetes, as a rule, has remained most deplorable in spite of the insulin. They have still had to endure, so to speak, a restricted existence. They have not been allowed to enjoy the pleasure of satisfying their hunger in a normal way, and they have still been treated as exceptions, which has been anything but advantageous especially with regard to their psychical development. To this very day many physicians have endeavored to keep the insulin doses down as far as possible, indeed, to try to carry on without insulin at least for some time, even if the diet must be extremely strict.

By degrees the views on this matter have changed. More and more the conclusion has been reached that children suffering from diabetes should be allowed to lead as normal a life as possible. Kirsten Utheim-Toverud, for instance, emphasized in 1931 the advantage of diabetic children's being allowed to share the food of their brothers and sisters, an advantage "which can hardly be overestimated in connection with a disease lasting for life." A similar point of view has been expressed by Friderichsen in his book on diet in 1933, in which he states: "Psychologically it is better to accommodate the doses of insulin to the food than vice versa."

The first who seems to have gone in deliberately for a quite free diet in connection with diabetes of children was Stolte, of Breslau, whose results published in 1931 seemed to be very favorable in a number of eases. In 1934 Söderling gave an account of some good results with similar treatment.

From the Pediatric University Clinic Kronprinsessan Lovisas Vardanstalt, Stockholm, Director A. Lichtenstein,

I personally have been using free diet for more than four years and in my teaching have consistently emphasized the importance of letting the diabetic child have a chance of living a normal life with free choice of food, and giving a sufficient quantity of insulin. By free diet I mean an absolutely free diet without any restrictions and without weighing the food or any of its ingredients. In other words, the children can fully satisfy their appetite and to some extent their individual taste, i.e., with regard to the supply of nourishment, and live a quite normal life. The only direction I give regarding the diet is to avoid luxury, which also ought to be avoided by healthy children.

The insulin is given in doses sufficient to keep the child in good general condition, in good increase of weight and free from ketone bodies in the urine. On the other hand, I have attached little importance to a somewhat greater or lesser sugar excretion, in ease the increase has not appeared in connection with a change for the worse in the general condition of the child or in the weight curve.

Up to the present I have used such treatment in about 50 cases, partly in the Kronprinsessan Lovisas children's hospital and in my private practice. The patients are children from the ages of two and one-half to sixteen years. Most of the cases have been followed for several years, the oldest one for fourteen years and most of the others from two up to eight years. A few cases have been early. All of them are to be considered as grave cases of diabetes in as much as in all of them coma, or threatening coma, has occurred once or repeatedly. The free diet has been carried through for a time varying from one-half to four-five years.

In most cases the children have been admitted to the hospital for the change to a free diet, and consequently I have been able to observe them thoroughly during that period. As a general opinion, I will first state that the change from the restricted to the free diet has always been very easy and has taken place without any disturbances.

It is a matter of course that the patients themselves and their families highly appreciate the release from strict dietary schedules and from the daily trouble of weighing and measuring the allowed quantity of food. But it is necessary to witness the joy of the diabetic children at the release in order to understand fully the psychologic importance of the free diet. The matter has a further importance. One obtains the definite impression that the altered psychologic sense, the release from being placed in an exceptional situation in relation to other children has a direct favorable influence on the disease of the patient.

As a first result of the release from restrictions we find that the children as a rule show signs of voracious hunger for carbohydrates. Very soon, however, the child spontaneously passes on to a more normal consumption of earbohydrates which varies but little. In doing so, however, the child always keeps the supply of earbohydrates on a higher level than previously. For instance, a boy of seven years, who had received

about 110 gm. of carbohydrates before being changed over to a free diet, consumed immediately after the change 300 gm. daily. After some time, however, he reduced of his own accord the consumption of carbohydrates to about 200 gm. daily. Instead of a supply of carbohydrates, which during the restricted diet was usually 90-110-130 gm., varying according to the age, the children have generally consumed, when the food is chosen on free impulse, 150-250 gm. daily and sometimes even more.

Any inconvenience on account of the increased supply of carbohydrates has not been observed. On the contrary, the condition of the patient has always been favorably influenced and often to a considerable extent. Even the weight curves have reflected improvement, no doubt depending upon the fact that not only the supply of carbohydrate but also the total supply of calories has, as a rule, increased in connection with the change to free diet. Thus children of from nine to twelve years of age, in which group most of my patients are found, have in connection with completely free diet, consumed from 50 to about 70 calories per kilogram and sometimes more.

It might be expected that the blood sugar level, as well as the carbohydrate excretion, would be increased to a great extent if the doses of insulin were not raised correspondingly. But this has not been the case. It is true that some patients on free diet have required larger quantities of insulin than previously, but the increase has usually been moderate and sometimes quite insignificant. In many cases the dose of insulin has been maintained unchanged without inconvenience, and sometimes it has even been possible to reduce it, in spite of the fact that the supply of carbohydrates has been twice the amount previously given. Similar observations were mentioned for example by L. Emmett Holt in 1933.

The blood sugar level has often proved to be more regular than previously, sometimes a little higher, but sometimes considerably lower, and at the same time more uniform. Nor has the urinary sugar excretion been considerably higher during the free diet, but sometimes remarkably low in proportion to the large supply of carbohydrates.

An inconvenience attached to the free diet seems to be that of the usual insulin generally three injections must be given in twenty-four hours, often in eases in which two injections were sufficient during the restricted diet. Only in rare instances have my patients been able to do with two injections in twenty-four hours in connection with free diet.

It stands to reason that the supply of insulin through injections always becomes stiff and schematic compared with the smooth variations in the production of insulin from a healthy pancreas. On the other hand, three daily injections make it possible to bring about, in the grave eases of diabetes, a better distribution of the insulin than two injections.

Instead of using the usual insulin we have during the last year more and more passed over to the use of Hagedorn's protamine insulin (insulin rétard). This preparation, a combination of insulin and

protamine, is absorbed much more slowly than the usual insulin. On account of this it has been possible to reduce the insulin doses from three to two, and in many cases even to only one injection per day, in spite of keeping the child on a free diet. The treatment of a difficult case of diabetes has been simplified as far as possible at present, when the patient, after having taken his insulin injection in connection with his morning toilet, needs to think no further of his illness until the next morning.

With free diet, at least according to my experience up to the present, the risk of an overdosage of insulin with consequent trouble and inconvenience is far less than with restricted diet. In only one of my patients, a boy with rather varying and sometimes bad appetite, have I observed symptoms of insulin shock in connection with free diet. In all other patients no such symptoms have been traced as yet.

A fact of great interest, and no doubt of great importance, is that the ketonuria disappears, or at least decreases considerably, after the change to free diet. Children, who had earlier always shown decided positive reactions to the Gerhardt and Legal tests and who in many instances had to be admitted to the hospital again and again with threatening or developing coma, have, after being placed on a free diet, been totally or almost totally free from these difficulties.

Further it is manifest that intercurrent infections, which are known to constitute permanent danger for the child suffering from diabetes, after the change to free diet generally have been overcome much more easily, and exert much less influence on the metabolism than is the case with restricted diet. As a consequence we have found that our diabetic children, who earlier were permanently returning guests at the hospital, often several times every year, now almost without exception can be easily eared for outside the hospital.

Although it is not my intention to enter into particulars with regard to case histories, I wish, however, to mention a case which gives, in my opinion, a good illustration of the advantages of the free diet.

A girl aged two and one-half years, whose diabetes had been diagnosed at the age of one and one-half years, was nursed from that time in a hospital for an entire year with strict diet and insulin up to 22 units. During the entire time the general condition was bad with permanent ketonuria and, as a rule, high acctone content. Further, symptoms of urinary infection were present. When taken in at the Kronprinsessan Lovisas Hospital, she was precomatic and showed pyuria and symptoms of infection in the upper respiratory tract with fever.

As soon as the coma had been overcome, she was placed on a free diet. The child consumed 62 calories per kilogram (about 100 gm. of carbohydrates) and received 34 (12+10+12) units of insulin. She improved rapidly so that the renal affection could be investigated through pyelography. It was found to be due to a stone the size of a hazelnut, which could be removed through pyelotomy. The child went through the operation well and was in condition after five weeks to be discharged on a free diet (about 80 calories per kilogram—70-80 gm. of carbohydrates) with 30 units of insulin (10+10+10), acctone-free, and with a good increase of weight.

This girl had been attended by a competent doctor in a hospital for an entire year, without her condition ever becoming sufficiently improved so that her renal affection could be investigated. After the change over to the free diet, it was possible, in the course of some weeks, not only to improve her general condition in such a way that pyclography could be tried, but the patient could also be operated upon for the removal of stone in the kidney and very soon be discharged in excellent condition.

As shown above, my experience with a completely free diet in connection with diabetes of children is up to the present very favorable. It is certainly true that the time of observation for some of the cases does not yet amount to a year and, therefore, for a disease such as diabetes, must be regarded as short. But the improvement has always been so obvious and, during months or in many cases up to four to five years, proved to be so permanent that I have found it advisable to make this experience known. My own opinion is that with a really free diet for the first time full advantage has been taken of the introduction of insulin in the therapeutics of diabetes.

# THE INFLUENCE OF A DAILY SERVING OF SPINACH OR ITS EQUIVALENT IN OXALIC ACID UPON THE MINERAL UTILIZATION OF CHILDREN

P. Bonner, F. C. Hummel, M. F. Bates, J. Horton, H. A. Hunscher, Ph.D., and I. G. Macy, Ph.D. Detroit, Mich.

BECAUSE milk, fruit, and green leafy vegetables contain protein of excellent quality, or a generous and well-balanced mineral mixture, and a supply of vitamins essential for life and well-being, they have been called "protective foods." As might be expected, green leafy vegetables vary in their content of vitamins and minerals depending upon the class and variety, the climate, the soil in which they are grown, and the way they are marketed and handled before consumption. On the other hand, little thought had been given until recently to untoward properties resident in the commonly used foods and their effects upon the organism. It is now known that some of these foods contain toxic substances, such as fluorine, selenium, and oxalic acid, which are toxic when taken into the body in sufficiently large quantities. These substances are not only present in small and variable amounts in foods, but might also be natural constituents of the body.

The realization of a relatively high oxalic acid content in spinach, in contrast to some of the other green leafy vegetables, and the deleterious effect of these amounts of oxalic acid upon calcium metabolism in the rat, has attracted renewed interest in its consequence in the metabolism of man.4-6 Although spinach has been used as a staple vegetable in the dietary of man, and for years has been placed on the diet list of practically every menu illustrating the adequate dietary for adult, child and infant alike, it is now being scrutinized anew. As a matter of fact, the majority of investigations on the nutritive value of spinach have usually been for a different purpose other than for a study of its deleterious properties in average servings and have included enormous quantities of spinach which are all out of proportion to actual dietetic practice. For instance consideration has been given to the availability of calcium4-9 and iron<sup>9, 10</sup> in spinach, the influence of its bulk<sup>8-10</sup> and its potential acid-base residue11 upon metabolism. To date the advantages usually accredited to the green leafy vegetables in general are increased gastrointestinal motility, improved appetite, the addition of vitamins and increased intake of minerals, particularly iron,

From the Research Laboratory of the Children's Fund of Michigan, and the Children's Village, Detroit.

Presented before the Division of Biological Chemistry at the ninety-second meeting of the American Chemical Society at Pittsburgh, Sept. 7-11, 1936.

The purpose of the present investigation has been to observe the influence of a daily serving of 100 grams of puréed spinach or its equivalent in oxalic acid upon the nitrogen, calcium, and phosphorus utilization of preadolescent children.

#### EXPERIMENTAL PROCEDURE

Subjects.—Ten children, aged five to eight years, were carefully selected because of an excellent health record since early childhood, according to the medical examinations.\* Their dietaries were controlled for seven months preceding the study of spinach in order to assure mineral reserves. During this time the subjects had demonstrated that they were good eaters, and were cooperative and happy in their environment. Each child was studied with and without spinach or oxalic acid, thus each child served as his own control.

In a previous publication<sup>12</sup> it was pointed out that in fundamental metabolic studies it is extremely important not only to select the subjects carefully in view of their nutritive condition, but to keep them "happy and interested in their wholesome regularity of personal habits, sleep, work, play, and in their healthful living in a home environment where love, security, and serenity abounded."

Dietary and Metabolic Procedure.—The daily intake of simply prepared common foods; was kept constant in quantity and quality for each child throughout the control and experimental periods except for the addition of 100 grams of canned spinach (purced to assure complete sampling of plant parts) during the latter periods. Each day for five days immediately following the spinach addition, and with the same basal diet, oxalic acid equal to that determined in the spinach fed, was given together with the calcium (calcium acetate) equivalent of the spinach. The basal diet had been used for a period of years in this laboratory and has been found to be satisfactory for children as indicated by their growth in height, weight, and gains revealed by frequent medical and physical examinations. Moreover, it was sufficient to promote nitrogen and mineral storage. The basal diet contained the equivalent of 90 to 100 U.S.P.X. units of vitamin D and 90 to 120 milligrams of ascorbic acid daily.

The calcium intake of eight of the children approximated 0.8 gram daily while that of the two eight-year-olds was 1.3 grams. The oxalic acid content of the 100 grams of spinach fed amounted to 0.7 gram. The calcium contributed by the spinach supplement represented only 5 to 7 per cent of the total intake. Since the free oxalic acid of the spinach will combine with the calcium of the other foods eaten simultaneously, any untoward effect on calcium retention will depend upon the quantity of spinach consumed and the adequacy of the calcium in the diet.

†List of common foods used in the basal diet:

Apple
Banana
Lean beef
White and whole wheat bread
Butter fat
Cabbage
Carrots
Cheese
Corn flakes
EEE

Graham crackers
Lettuce
Milk
Orange juice
Peanut butter
Potato
Shredded wheat
Sugar
Tomato juice

<sup>\*</sup>Marsh W. Poole, M.D., pediatrician at the Children's Village, not only attended the children during the present study and made all the medical and physical examinations but he had followed them at regular and frequent intervals for several preceding years.

The skeletal structure and maturity of the children were kindly evaluated by T. Wingate Todd, M.D., and C. C. Francis, M.D., of Western Reserve University, Cleveland, according to their highly specialized and standardized x-ray technique and interpretation.

TARLE I

Anbrigh Dalix Callina, Phosphores, and Netrogen Referitor Dering Consumption of a Control Dile, With a Supplyable of 100 Grans of Dalix, Chemis Der Duked Spinach or Its Oxide Acid Equivales (Grans Der Day)

	BILINCE	5.33 5.28 5.82 7.73	0.18 0.50 0.98 0.34	0.95 1.00 1.34	0.65 0.75 0.87 0.90	0.59 0.80 0.76 0.95
N.		1.11 0.108 1.03 0.99	1.30 0 1.32 0 1.19 0 1.21 0	1.16 0 1.16 1 1.29 1	0.98 0 0.90 0 0.90 0	1.09
NITROGEN	TENTE	9.06   1 9.19   1 8.71   1 8.73   0	9.02 9.03 8.39	8.37 8.70 7.88	8.40 8.94 8.68 0.55	8.34 8.82 8.61
	ENTAKE	10.19 10.85 10.56 10.15	10.19 10.85 10.56 10.15	10.49 10.85 10.45	10.02 10.74 10.45	10.02 10.74 10.45 10.45
	BYLASCE	0.082   1 0.111   1 0.075   1	0.062 1 0.164 1 0.104 1 0.051	$\begin{array}{c c} 0.137 & 1\\ 0.157 & 1\\ 0.184 & 1 \end{array}$	0.134   1 0.140   1 0.064   1 0.106   1	0.093 0.141 0.028 0.126
ORUS	reces	0, 138 0, 153 0, 153 0, 138	0,509 0,183 0,416 0,190	0.290	0.280 0.338 0.293 0.332	0.298 0.356 0.316 0.316
PHOSPHORUS	DRINE	0.587 0.635 0.591 0.570	0.537 0.555 0.572 0.551	0.679 0.726 0.630	0.618 0.697 0.738 0.657	0.641 0.678 0.807 0.653
	SMATKI	1.107 1.202 1.122 1.095	1.107 1.202 1.122 1.095	1,107 1,202 1,095	1.032 1.175 1.095 1.095	1.032 1.175 1.095 1.095
	BALANCE	0.140 0.170 0.113 0.113	0.107 0.147 0.134 0.115	0,175 0,202 0,180	0,146 0,163 0,184 0,184	0.123 0.161 0.170 0.202
TOX	PECES	0.567 0.592 0.610 0.519	0.616 0.635 0.661 0.612	0.522 0.552 0.526	0.530 0.583 0.582 0.582	0.568 0.610 0.615 0.520
CALCIUM	ORIZE	0.062 0.069 0.05 t	0.016 0.018 0.012 0.019	0.071 0.076 0.069	0.077 0.079 0.066 0.070	0.062 0.054 0.017 0.053
	BALTKE	0.768 0.830 0.837	0.768 0.830 0.837 0.837	0.768 0.830 0.773	0.753 0.825 0.832 0.775	0.753 0.825 0.832 0.775
×	DVAE OBSEKAVLIO		និងក្នុង	25 10 10	55 55	12 2 2
	WEIGHT*	23.53 23.53 23.54	22222 614764	23.0 23.6 23.4	21.5 22.1 22.3 23.3	19.3 19.7 19.9 20.0
	невент* (см.)	119.8 119.8 119.8	119.4 119.7 119.9 120.0	117.4 117.9 118.6	116.3 116.5 116.8 116.8	110.9 110.7 110.7 110.7
	VGE*	82/12 83/ 8 83/23 83/23	88/ 0 88/25 89/11 89/16	80/ 6 81/ 2 81/27	77/ 6 78/ 2 78/17 78/22	71/15 72/10 72/25 72/30
	DILTARY	Control I Spinneh Oxnlie acid	Control I Spinneh Oxalic neid Control II	Control I #Spinneh #Control II	Control I Spinach Oxalic acid Control II	Control I Spinach Oxalic acid Control II
	сипр	F. C. (M)	H. H. (M)	P. W. (F)	J. M. (T)	B. F.

TABLE I-CONT'D

																		1	
	BYLANCE	0.84	0.91	1.02	0.61	0.45		0.73	0.48	2 - -	0.89	10.1	33.		12.0	0.43	9.5	0.48	
GEN	FECES	1.17	1.00	1.05	0.97	0.82	3	1.15 1.15 1.15	111	1.05	1.23	1.50	1.13	1	1.06	1.33	0.98	I.E	
NITROGEN	URINE	8.12	8.45	8:38	7.75 8.25	8.17		8.08 7.08	8.86	3. 1.	10.22	10.42	10.10		11.07	10.90	11.04	10.73	
	IXTAKE	10.12	10.44	10,45	9.32	14.0 0	1	10.12	10.45	10.45	12.34	12.70	14.21	15.7	12.34	12.66	13.41	12.41	
	BYLANCE	0.106	0.089	0.085	0.067	0.0.19	0000	0.112	0.010	0.111	0.1.40	0.199	0.160	Corro	0.208	0.159	0.000	0.115	
ORUS	FCES	0.296	0.337	0.295	0.269	0.2.19	001.0	0.314	0.330	0.316	0.465	0.461	0.363	707.0	0.440	0.436	0.334	0.451	
PHOSPHORUS	nerxe.		0.749	_	0.680			0.000	0.766	0.668	0.886	0.923	0.080	1.00.0	0.843	0.952	1.070	0.937	
	NAVKE	1.199	1.175	1,095	1.020	1.008		1.133	1.095	1.095	1.491	1.583	1.503	1.000	1.491	1.547	1.503	1.503	
	SALANCE	0.178	$0.176 \\ 0.176$	0.170	0.176	0.155	cor.o	0.098	0.136	0.163	0.148	0.172	0.183	).TT.0	0.175	0.174	0.149	0,151	
LUM	ECES	10.524	0.526	0.467	0.528	0.548	0.483	0.004	0.6002	0.532	1.020	1.068	1.075	166.0	0.946	1.002	1.025	0.978	
MUIOIUM	BINE	0.102	0.123	0.138	0.070	0.080	0.097	0.102	0.100	0.000	0.082	0.077	0.066	0.070	0,138	0.138	0.150	0.138	en.
	NTAKE	-			0.77.4	0.792	0.733	0.804	0.835	0.775	1.259	1.317	1.324	1.267	_	1,314	1,324	1.267	v regin
	VXS VXS		ម្រ	15 0	81 t	ည	15	20	ig v	12.	10	12	10	15	50	0 <del>†</del>	ນລ	15	f dietar
	eight* cg.)	r)	18.7	18.7	17.8	18.4	18.6	19.4	19.8	19.8	27.6	87.5	25.0	25.1	2 20	27.9	28.6	28.4	nning
	TH913	о) нн	107.5	107.6	106.0	106.4	106.7	114.8	115.2	115.6	1107	110.1	119.5	119.6	136.2	136.4	136.9	137.0	for hor
	*3	ZO VQI	59/25 60/19	61/5	67/11	68/ 5	68/35	06/09	70/16	0 /12	71.00	100/13	100/27	101/1	1007	100/001	104/20	104/13	tone alon for hoginning of dictory regimen.
	DIETARY		Control I	Oxalic acid	Control T	Spinneh	Control II	T London	Spinach	Oxulic neid Control II		Control 1.	Oxulic neid	Control II	F (21)	Spinsol	Overlin anid	Control II	And holy ond welcht o
	CHILD		J. H.	(m)	25	E		e o						-	د د	.3.7.			tot on V.

\*Age, height, and weight are given for beginning of dietary regimen. †P. W. was removed from study during three periods.

The food, urine, and feces were collected quantitatively and analyzed for nitrogen.13 calcium,14 and phosphorus15, 16 in successive five-day balance periods.\*

#### RESULTS AND DISCUSSION

One hundred and twenty-one five-day metabolic balances (605 days) for each of nitrogen, calcium, and phosphorus have been made on ten growing children and are presented in Table I. The individual physiologic response characteristic for each child has been determined for sixty successive days on eight children and for forty-five days on one child. During the initial period of twenty-five days the children consumed the basal diet which was immediately followed by fifteen days on the control diet with a supplement of 100 grams of spinach daily, then five days on the same diet in which oxalic acid and calcium were substituted for their equivalents in 100 grams of spinach daily, and finally fifteen days on the basal diet. The tenth child, an eight-year-old boy, D. P., was observed for a period of eighty-five consecutive days, the first twenty-five days of which he received the constant controlled food intake which was followed by forty days with a dietary supplement of 100 grams of spinach daily, five days with oxalic acid and calcium substituted for the spinach and lastly fifteen days on the control diet.

The average daily amounts of nitrogen, calcium, and phosphorus ingested and excreted in the urine and feces, from which the quantity retained per day for each child is determined, during the successive dictary regimens are recorded in Table I. The storage rates of these elements were not significantly altered by the daily addition of 100 grams of spinach, and moreover, they are compatible with the normal variations of these elements observed in growth. The differences between the average daily storage for the initial twenty-five-day control period and the fifteen to forty-five days on spinach ranged from -0.26 to +0.32 with an average difference of +0.06 gram of nitrogen, -0.045 to -0.040 with an average of  $\pm 0.015$  gram of calcium, and -0.049 to  $\pm 0.102$ with an average of +0.019 gram of phosphorus for the ten children. Furthermore, the daily substitution of the oxalic acid and calcium equivalent of 100 grams of spinach gave variable results but ones that cannot be interpreted as indicating a deleterious effect. Since this amount of oxalic acid was distasteful, and the results were more academie than practical, only one five-day balance period was secured. From a practical consideration in dietetic management spinach would be fed less frequently, certainly not every day in so generous a serving. From these results, spinach cannot be considered harmful to children of this age group, even in daily servings of 100 grams. This conclusion is further verified by the fact that no cumulative toxic or untoward

<sup>\*</sup>The metabolic balances for magnesium, potassium, sodium, chlorine, sulfur, and iron will be reported at a later date.

effects could be detected in the average daily nitrogen, calcium, and phosphorus assimilation during the periods of spinach or oxalic acid consumption, nor during the control periods immediately following. Furthermore, no deleterious effects were revealed in a large number of other types of physical, chemical, and physiologic measurements.

In this study of the physiologic effect of a daily serving of 100 grams of spinach upon the utilization of nitrogen, calcium, and phosphorus, the

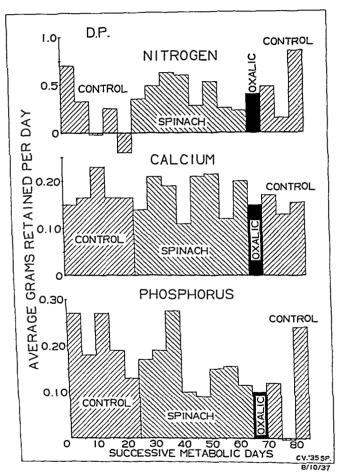


Chart 1.—The increments and decrements of storage of nitrogen, calcium, and phosphorus of an eight-year-old boy during a period of eighty-five days, a part of which included observations on a control diet alone, or with a supplement of 100 grams of spinach daily or its oxalic acid equivalent.

spinach was superimposed upon a diet which had promoted good growth and storage in these same children for several months immediately preceding. The plan herein adhered to was different from those of other investigators who observed the relative availability of the calcium present in spinach as compared with that in milk<sup>4, 6</sup> and over shorter periods

of time. As a matter of fact, green leafy vegetables are not given as a source of calcium, but for other nutritive purposes such as for iron,<sup>9, 10</sup> vitamins,<sup>1</sup> acid-base mineral mixture,<sup>11</sup> or even bulk.<sup>8-10</sup>

Because each child has an individual physiologic growth performance which varies from time to time as maturation proceeds,<sup>17</sup> it is essential in biologic assay of foods to have adequate test periods.<sup>12</sup> Chart 1 shows the increments and decrements of storage of nitrogen, calcium, and phosphorus that may be observed in healthy growing individuals maintained under strict metabolic conditions provided they are followed continuously over a considerable period of time. D. P., an eight-year-old boy, demonstrates the inconsistency of chemical growth and the average daily storage rates characteristic of childhood and illustrates why "it is neces-

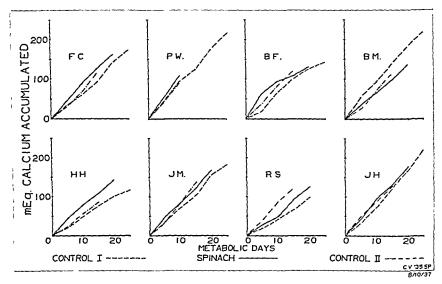


Chart 2.—The cumulative calcium balances for eight children for the initial control dietary, for the spinacn, and the final control regimens.

sary to learn throughout a pre-experimental period of several weeks how wide these customary individual rates of storage under highly standardized and desirable conditions before the effect of any regimen upon the metabolic balance can be satisfactorily understood. Without the inclusion of such controlled data one may be easily misled into false fields of interpretation by the use of this method for determining the subsequent effect of certain foods or other factors on metabolism."<sup>12</sup>

Cumulative Storage.—Since the duration of the experimental observations of this investigation extended over sixty to eighty-five continuous days, a new type of interpretation has been permitted which is particularly significant in the consideration of physiologic adjustments that may occur coincident with a change in dietary regimen and, most important, in case of a possible toxicity, an opportunity is given to record its cumulative effect upon metabolism, i.e., the progressive gain or loss of a particular element over a period of time. The cumulative interpretation of metabolic data shows the progress of growth and any variation therefrom. In addition, it indicates the immediate effect of a dietary shift as well as the gradual metabolic adjustments that a change in dietary regimen may promote. This is illustrated in the cumulative calcium balances for eight of the children for the initial control regimen, for the spinach, and for the final control period as given in Chart 2. Average daily balance data may mask the alterations in rate of storage of an element (Table I). Spinach neither changed the rate of storage of calcium during the twenty- to forty-day period of its consumption now showed a deleterious after-effect during the subsequent fifteen-day control period.

Effect of Spinach on Fecal Outgo.—Although the dry weights of the feces were higher during the ingestion of 100 grams of spinach daily than during the control and oxalic acid periods, there was no consistent increase in calcium outgo in relation to fecal mass. Furthermore, the increased bulk due to the spinach did not accelerate gastrointestinal motility as measured by frequency of defecation, time of appearance of marker, or the wet weight of the feces.

#### SUMMARY

- 1. One hundred and twenty-one metabolic balances for each nitrogen, calcium, and phosphorus have been made on ten growing children. The individual physiologic response characteristic for each child on the different dietary regimens has been determined for sixty to eighty-five successive days by five-day balance periods. Each child served as his own control.
- 2. Control periods of twenty-five days on the ordinary mixed diet of common foods showed the children to be storing nitrogen, calcium, and phosphorus. The storage rates of these elements were not significantly altered by the daily consumption of 100 grams of spinach; moreover, they were compatible with normal variations observed in growth.
- 3. No cumulative toxic or untoward effects could be determined either in the average daily retentions, or in the progressive storage curves of nitrogen, calcium, and phosphorus either during the period of consumption of spinach and oxalic acid or during the control period immediately following.
- 4. The supplementation of an already adequate diet with a generous serving of spinach daily, even for as long as forty consecutive days, did not change the rate of calcium storage in growing children when their calcium intake was adequate to cover the precipitating effect of the oxalic acid and provide for their fluctuating growth needs.
- 5. The practical conclusion drawn from the data recorded herein is that spinach is not harmful even in servings of 100 grams daily, at least

in preadolescent children, but because of its richness in vitamins, minerals, especially iron, and other nutritive essentials it should retain its customary place along with other green leafy vegetables.

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# TOXIC ENCEPHALOPATHY IN A CHILD FOLLOWING THE INTERNAL ADMINISTRATION OF POTASSIUM CHLORATE AND SULPHARSPHENAMINE

JOSEPH GREENGARD, M.D. CHICAGO, ILL.

UNDER certain circumstances it is justifiable to use toxic drugs therapeutically. There are relatively mild conditions, however, in which such measures are employed at times by physicians in their zeal to "do something." One of these conditions is ulcerative stomatitis caused by the Vincent's organism in which oxidizing agents are usually employed. Of these sodium perborate, hydrogen peroxide, and potassium chlorate are frequently used. In addition spiracheticidal drugs such as the arsphenamines have been used both locally and internally. As a general rule this type of stomatitis is readily amenable to therapy and heroic measures are seldom necessary. For this reason a case is here reported in which severe toxic symptoms followed the use of potassium chlorate and sulpharsphenamine.

B. G. a four year old white child, was seen the evening of September 19 with the complaint of repeated vomiting and muscular weakness since that morning. Ten days previously the child had developed a sore mouth which was diagnosed as trench mouth by a physician who prescribed a solution to be applied with swabs and gave the child 0.2 gm. sulpharsphenamine intramuscularly The latter medication was repeated three days later and at that time, because the child would not cooperate with the swabbings, a saturated solution of potassium chlorate was prescribed to be administered internally in teaspoonful doses every This latter medication was continued for an entire week. For several days prior to the onset of vomiting the child had taken very little food but had been up and about the house as usual. On the morning of the nineteenth the child began to vomit and emesis continued repeatedly throughout the day, consisting first of curdled milk but soon becoming green. About 10 A.M difficulty in walking appeared, the gait became staggering, weakness progressed until the child remained in bed and would not even assume a sitting position. A brother, aged six years, also developed a sore mouth which was called trench mouth and received similar treatment with the exception of the internal admin istration of potassium chlorate.

B had been a premature infant weighing 3 pounds at birth and 18 pounds at the end of the first year. Development was normal. In 1935 she had had an uncomplicated scarlet fever. A tonsillectomy had been done in August, 1936 The past history was otherwise negative.

The initial physical examination revealed a rather thin, pale, child who was conscious but appeared somewhat discriented. She was very irritable and resisted examination especially of the mouth. Both upper extremities showed definite paucity of movements and were maintained in a semifleved position

with the elbows flexed and the hands partially flexed. Though tonus was good the extremities did not react normally, there being no defense movements and no attempt at grasping objects. The legs showed no paralyses; tendon reflexes were present and hyperactive; there were no pathologic reflexes. There was definite head drop and weakness of the muscles of the back, the patient slumping on attempting a sitting position. There was no rigidity of the neck or back and no abnormalities of sensation could be determined. The pupillary reflexes and ocular movements were normal. There were a few scattered aphthae on the buccal mucosa but no true ulcerative or gangrenous lesions. Examination otherwise was negative.

At this time an atypical poliomyelitis was suspected but the possibility of a potassium chlorate poisoning was also entertained. The child was taken to the Michael Reese Hospital for spinal puncture and further observation and treatment. The spinal fluid was water clear under normal pressure, tests for globulin were negative, and there were ten lymphocytes present. This finding excluded poliomyelitis and the diagnosis of probable potassium chlorate poisoning was made. Blood and urine samples were taken for methemoglobin and the child was placed on continuous intravenous drip therapy with 10 per cent glucose in normal saline.

Her subsequent course in the hospital pointed to severe central nervous system involvement. The child was stuporous, did not talk or swallow, nor did she seem to recognize her mother. On September 21 periodic short convulsive spasms appeared. The pupils dilated, the eyes deviated to the right and clonic twitchings of the face and extremities occurred repeatedly at short intervals. Chvostek's sign was present and there was typical carpal spasm. Head drop was still present but there were no definite paralyses. Calcium gluconate, 15 grains intravenously twice daily, and calcium bromide, 10 grains three times daily by mouth, were administered. That evening there was little improvement, and the twitchings continued. An intravenous transfusion of 160 c.c. whole blood was given and the drip clysis of normal saline and 5 per cent glucose continued. The following morning she was much quieter. Chyostek and Trousseau's signs were negative, her neck was not rigid. The face appeared slightly edematous and distinctly dusky. She was in a deep stupor and would swallow nothing. Feeding by gavage was instituted. On this date the urine was disdirectly pink in color, yielded a 4+ benzidine reaction but contained no red corpuscles.

From this time on (Sept. 23, 1936) the child slowly improved. She continued semistuporous, did not recognize her mother or father, but did seem to recognize nurses and doctors and resist their attempts to examine or treat her with violent struggling and screaming. She made no attempts to speak and was entirely unable to swallow. Tube feedings, however, were carried out successfully and the intravenous clysis was discontinued. The eyegrounds were normal at all times.

On Sept. 27, 1936, spinal puncture was repeated. Fluid was water clear and normal except for a colloidal gold curve up to four in the midfield. On this date she was examined by Dr. Roy Grinker who noticed an athetosis of both upper extremities, slight spasticity of the left arm and a + left Chaddock sign. Otherwise there were no findings. He felt the condition was in the nature of an encephalitis with the lesion predominantly in the basal ganglia, the etiology in his opinion being arsenical from the sulpharsphenamine.

From this time the child seemed quieter but still did not recognize or respond to relatives and could not swallow or sit up. October 3 another spinal puncture was done. Fluid was clear, under normal pressure, Pandy was definitely positive,

there was no increase in cells and sugar was 68 mg. per cent. On October 4 the child attempted to swallow for the first time, seemed to recognize her mother and smiled occasionally. She was also able to sit up alone.

October 10 she was examined by Dr. Lewis J. Pollock in consultation. He considered the case a pseudobulbar type of encephalitis, bilateral and deep seated, etiology toxic; but he did not feel it was arsenical since it did not resemble arsenical cases in his experience. Whether potassium chlorate was responsible he felt could not be proved or disproved.

From this time improvement continued very slowly. By Oct. 12, 1936, she was swallowing much better. On October 22 she was much brighter, swallowed well and said "No, No" and "Ouch," her first distinct words. She was able to stand and walk, but still could not use her fingers or hands well and showed her "rage reactions." The following day she was discharged from the hospital.

Laboratory findings while in the hospital were as follows: The urine was constantly negative with the exception of the presence of hemoglobin on the day following the transfusion. Blood showed a moderate anemia, but otherwise no noteworthy findings. The blood Wassermann was negative, blood sugar 49 mg. per cent: nonprotein nitrogen 32, and calcium 9.5 (after calcium administration). The icterus index was 11, van den Bergh direct 0, indirect immediate positive. The spinal fluid was as noted above and in addition revealed a sugar of 62 mg. per cent and a colloidal gold curve on one occasion of 0012444321. Hair and nail parings were negative for arsenic.

October 27 she was examined at home. She was doing quite well but still said no words. She walked normally, used her hands better but still had difficulty in apposing the fingers and thumb. The right knee jerk was exaggerated and there was unsustained right ankle clonus. She was given a tonic containing iron and vitamin B.

November 7 she was reexamined. Her progress had been satisfactory. She seemed to understand everything and tried very hard to talk. On examination she was quiet and cooperative, responded to all questions and directions, and said "yes" distinctly. She used her fingers and hands well. Neurologic examination was negative.

December 20 she was seen again. She was now saying everything and as far as the mother was concerned was perfectly normal.

She was again examined on March 27, 1937. She had developed a cough three weeks previously which turned out to be pertussis. Other than this the child had been doing well. Her speech, however, was very slow and careful in character; her facies was definitely mask-like, but there was no propulsive gait and no tremor.

#### COMMENT

The striking feature of this history is the administration of two toxic drugs to a small child with a presumable Vincent's stomatitis, sulpharsphenamine in two doses of 0.2 gm. and potassium chlorate in a total dose of 7-8 gm. During the course of this therapy the child developed evidences of a severe intoxication, the predominant symptoms of which soon pointed to involvement of the central nervous system. Which of these two drugs was responsible or whether the damage was due to their combined action is difficult to state. A careful review of the literature fails to reveal any report of central nervous system involvement as a part of potassium chlorate poisoning. Certain features of the acute symptomatology at the onset do fit in with such poisoning, however.

Gettler and St. George<sup>1, 2</sup> cite a case of fatal poisoning in a three-year-old boy in whom potassium chlorate solution had been prescribed as a gargle over the telephone. The mother misunderstood the directions and administered the solution by mouth with severe acute symptoms appearing after several doses followed by death in six hours. At autopsy the blood was chocolate brown and showed methemoglobin spectroscopically. The stomach was not corroded but was a slate gray color, all the organs were congested and grayish brown in color. The kidneys showed a parenchymatous nephrosis microscopically. Ansbacher<sup>3</sup> states that fatal potassium chlorate poisoning is rare at present. He reports a case in which the drug was taken by a young woman resulting in death. Bernstein<sup>4</sup> reported the case of an insane army officer who ate the entire contents of a tube of Pebeco tooth paste corresponding to about 7.5 gm. of potassium chlorate.

Cushny<sup>5</sup> states that the lethal dose of potassium chlorate varies greatly, as little as 1 gm, having proved fatal in a child while 40 to 50 gm, have been swallowed by adults without marked symptoms. McGuigan6 also gives the minimal fatal dose as 1 gm. but states that in general 10 gm. or more are necessary to induce poisoning and 15 to 30 gm. are usually fatal. Gettler and St. George place the average fatal dose at 3 to 5 gm. According to Cushny, acute chlorate poisoning is first evidenced by severe and persistent vomiting with epigastric pain, diarrhea, and a dark evanotic color of the skin and mucous membranes. Respirations are dyspneic, the pulse is rapid, feeble, and at times irregular, headache, giddiness, muscular weakness and restlessness supervene, and eventually in fatal cases coma and death follow. In the subscute cases vomiting and diarrhea are prominent, the vomitus frequently being bile stained, and sometimes bloody. The urine may be completely suppressed, or may be scanty and dark colored, later reddish brown containing hemoglobin, methemoglobin, and hematin in solution. The skin is often ieteric and uremic symptoms may appear.

The action of potassium chlorate is on the red blood cells and especially on the hemoglobin with the formation of methemoglobin and hematin; laking occurring with the freeing of methemoglobin into the plasma. This action is due to the oxidizing property of chlorates. As a result asphyxia occurs and is the chief cause of the symptoms. In subacute cases products of red cell destruction obstruct the tubules of the kidney and in these cases fatality may be due to renal changes. Some of the products of hemoglobin destruction are deposited in the liver and spleen and bile pigments are increased in amount resulting in jaundice. Cushny states that chlorates have little or no direct effect upon the central nervous system or circulation though these are secondarily influenced by the asphyxia and renal changes. McGuigan says that fatality in neute cases may be attributed in part to potassium action on the heart and that fragmentation of heart muscle is a frequent cause of death.

The sudden onset of severe vomiting and marked muscular weakness in a child who had been receiving approximately 16 grains of potassium chlorate daily by mouth for a week or more is certainly significant. On one occasion the urine contained hemoglobin but inasmuch as this followed a blood transfusion it is difficult to consider it confirmatory evidence. An immediate positive indirect van den Bergh was also obtained. When this is combined with a complete lack of other findings to explain the severe symptomatology one is forced to attribute more than mere coincidence to the use of the potassium chlorate. The central nervous system involvement appeared to be definitely of a toxic rather than inflammatory nature. While it is impossible to incriminate either of the drugs positively one is inclined to suspect a possible causal relationship between one or both and the cerebral injury.

The reason for this report is to direct the attention of the medical practitioner to a major disaster which followed the internal administration of potassium chlorate in the treatment of a stomatitis. Lust in discussing the use of potassium chlorate in Vincent's angina calls attention to its toxic properties with the statement "because of its marked hematoxic properties it is best to eliminate this drug entirely from pediatric practice and substitute for it harmless preparations. . ." Cushny similarly comments that it was introduced into therapeutics on the crroneous theory that it would supply oxygen to the tissues, that it hardly retards the growth of bacteria and no adequate explanation for its use in mouth and throat infections can be offered. In contrast to these statements, is that in Stevens' Therapeutics:8 "In ulcerous stomatitis this salt is almost specific and may be used internally as well as locally. The dose for a child of three years is from 1 to 2 grains well diluted, every three hours. Benefit from its internal administration is to be attributed to its continuous elimination in the saliva." He does caution against its use in diphtheria and searlet fever because of renal irritation. Such a statement appears to me to be most unfortunate. physician who prescribed this medication said he had looked the subject up in Holt's Diseases of Children where he found a recommendation similar to the above. If so it must have been an old edition since the most recent revision by Holt and McIntosh<sup>9</sup> makes no mention of the internal administration of the drug and definitely states that locally the use of sodium perborate is preferable. I feel a revision of discussions on the therapy of stomatitis is in order with a definite warning against the internal administration of potassium chlorate and a caution as to its local use as well as the statement that systemic administration of arsenieals is hardly necessary in the average case. This child fortunately did not succumb but whether or not she will escape without residual changes still remains to be seen.

#### SUMMARY AND CONCLUSIONS

- 1. A severe toxic encephalopathy followed symptoms of acute poisoning in a child who received potassium chlorate by mouth and two injections of sulpharsphenamine in the treatment of a stomatitis.
- 2. While the literature contains reports of cases of accidental poisoning with potassium chlorate, an incident such as this with a resultant encephalopathy could not be found.
- 3. The causal relationship of the encephalopathy to the drugs used is not proved but is at least highly suggestive.
- 4. Potassium chlorate should never be administered internally in a child and its local use should be approached with caution. there is justification for its complete removal from the pediatric armamentarium since other more efficient and innocuous oxidizing agents are available.
- 5. The necessity for prompt and bold action on the part of physicians is recognized. There are situations, however, where expectancy is eminently more desirable than action which carries harmful potentialities. The adage "primum nihil nocere" should still be earried uppermost in the physician's consciousness.

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4753 BROADWAY.

### CHOLECYSTITIS IN CHILDHOOD

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WHILE it is generally stated that cholecystitis is rare in children there have been over 300 such cases reported. Potter<sup>1</sup> in 1928 collected 226 cases, Holbrook<sup>2</sup> in 1934 added 27 more, Powers and Scheidell<sup>3</sup> in 1935, 14 additional, and Zelditch and his collaborators<sup>4</sup> in 1936 reported 32 cases. In addition there are numerous individual reports. It is the opinion of those who have discussed this subject that affections of the biliary passages in children are quite frequently responsible for recurrent abdominal pain.

The purposes of this presentation are to review briefly the cases of cholecystitis in children which have been observed at the Children's Hospital of Cincinnati and in the pediatric service of the Cincinnati General Hospital during the past twelve years, and to emphasize the essential features of the condition.

The present series comprises 8 cases (Table I). This is not an impressive number to have been admitted to two large institutions over a period of twelve years. It is probable that a much larger group, milder in degree, had been seen, often without recognition, in the outpatient department. Several additional cases observed are not included because of inadequate confirmatory evidence.

In the cases reported the primary complaint was abdominal pain. This varied in intensity and was usually located in the hypochondrium, particularly on the right side. Many of the reports in the literature stress the fact that the pain was in the region of the umbilicus and was referred to the right subcostal angle. In cases reported by Snyder, Farr<sup>5</sup> and others, there were associated mild inflammatory changes in the appendix, and in these the pain was more indefinite in its localization and frequently more manifest in the right lower quadrant. The character of the pain may vary from a dull ache to intense cramp-like sensations. Nausea and frequently vomiting are accompanying symptoms, and there may be fever in varying degree.

Physical examination of these patients demonstrates tenderness and rigidity, more marked on the right side and usually in the upper quadrant. Varying degrees of jaundice may be present but it is more commonly absent. In some cases a tender mass may be palpated over the region of the gallbladder. In others the liver may be slightly enlarged. A moderate polymorphonuclear leucocytosis is usually associated.

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# Table I Case Presentation

	TIOSON	Recovered following repeated bite drain- ages.	Recovered following conservative treatment and appendectomy.	Recovered following cholecystectomy.	Recovered following cholecystectomy.
	HOW DIAGNOSED	Symptoms. Biliary returns.	Symptoms. Cholecystography. Operation: Gallbladder distended. Appendix normal.	Symptonis. Operation: Gallbladder thick, distended, and adherent to the paneren: which was swellen and indurated. Spleen enlarged.	Operation: Gallbladder Recovered thick, distended, and cholecyst filled with stones. Acute hemorrhagic puncreatitis with bloody fluid in peritonend cavity.  Appendix normal.
The state of the s	HEE DRAINAGE	Six.  Bile turbid with mucus, floccules and leucocytes. Culture—Typhoid.			
and the state of t	EXAMINATION	attacks of up Marked abdominal tender Six.  dominal pain, ness and rigidity, mostly Bile turbid with Biliary returns.  er. Recent at. in RUQ. Temperature leacocytes. Culture 102° F. WRCI 10,500.  Polys 84%.	nal pain, nausea, ness and slight rigidity in ROO.  13, and slight RUQ. Tonsils inflamed. Temperature 99° F. WRC 13,500. Polys 70%. Oral eholocystography — gall-bladder not visualized.	nattack of upper Marked tenderness in RUQ None.  nat pain, nausen,  ng, and fever.  ng car for three Attacks recurred  in, and localizing  or and localizing  ng car for three Attacks recurred  ng callbladder  ng callbladder  visualized  normally.	attacks of up. Marked generalized abdom None. dominal pain, inal tenderness and rivomiting and gidity in the right lower quadrant. Temperature 101° F. WBC 12,400.
	HISTORY	Recurrent attacks of upper abdominal pain, nausea, vomiting, chilis and fever. Recent attack of typhoid fever.	Recurrent attacks of upper abdominal pain, nausen, vomiting, and slight fever.	Sudden attack of upper abdominal pain, nausen, voniting, and fever. Draining car for three years. Attacks recurred in hospital, exaggerated by food, and localizing in RUQ.	Recurrent attacks of up- per abdominal pain, nausea, vomiting and fever.
	NGE 1N YEARS	<u> </u>	<u>=</u>	Π	11
	SEX	Female Colored	Female White	Male White	Femulo Colored

2.	on bridge a	MU MITCHELL: CHOLECISITY	15 2	209
Recovered following r appendectomy.	Recovered following appendectomy.	Apparent clinical recovery following cholecystectomy. Symptoms were temporarily relieved by bile drainage.	Recovery following thoracotomy and cholecystectomy.	
Cholecystography. Operation: Gallbladder markedly distended. Appendix chronically discased.	Operation: Gallbladder Recovered markelly distended. Appendix chronically discased and subhepatic in location.	Symptoms.  le turbid with Cholecystography. mucus, floccules and Bile drainages. leucocytes. Numer-Operation: Chronic adhesions much lepatitis, and hepatitis, tonitis, and hepatitis. Culture negative. Adhesions at base of gallbladder. Appendix normal.  Liver enlarged. Spleen 3 times normal size. No Lambia found in gallbladder contents. Culture—no growth.	Symptoms. Operation: Gallbladder thick, distended, and necrotic in several areas. It was adherent to the duodenum.	
None.	None.	More Fifteen.  More Bile turbid with Cholecystography. Ques.  mucus, floccules and Bile drainages. Fortal leucocytes. Numer. Operation: Chron cus motile Lamblia tonitis, and Stool  Myde.  Culture negative. Adhesions at base bladder. Apper and holia  Adhesions at base bladder.  Adhesions at base bladder.  Adhesions at base bladder.  Stool  Stoo	None.	-
And slight fever usually duestionable mass in occurring two to three hours at t.e. meals.  Marked constipation.  Marked constipation.  Marked pinn, nausea needs n	upper Marked abdominal tender-None. ausea, ness and slight rigidity farked in RUQ. Slight jaundice. Slight Temperature 100° F.; mable WBC 8,500; Polys 62%.	Recurrent attacks of ab- dominal pain, nausea, voniting, chills and fever usually occurring fever usually occurring firer meals. Marked constipution. Question- able jaundice.  Intestinalis. Oral dolo- cystography —gallbladder fireric acaions during attacks; normal visualized on two occasions during attacks following blie drainare.	kedly disked tenderity in RUG.	-
Recurrent attacks of upper abdominal pain, nausca and slight fever usually occurring two to three hours after meals.  Marked constipation.	Severe attack of upper abdominal pain, nauses, and vomiting. Marked constipation. Slight f ever. Questionable jaundice.	Recurrent attacks of abdominal pain, nausea, voniting, chills and fever usually occurring after meals. Marked constipation. Questionable jaundice.	Onset of right upper ab A dominal pain and tenderness during course of severe lobar pneumonia and empyemia thoracious. Numerous tarry stools.	*RUQ-right upper quadrant of abdomen,
15	=	c.	9	ght up
Female White	Female White	Маlс Агто- ліап	Male White	*RUQ-ri

tWBC-white blood cell count.

In five of our patients there was an associated infection of the respiratory passages. Focal infection is thought by most authors to be the exciting cause of cholecystitis, both in children and in adults. Beals,7 who reviewed 64 cases in children, supports this theory and believes that it especially applies to children. Snyder5 and Farr6 believe that many cases develop as a metastatic complication of a chronically or subacutely inflamed appendix. In two of our own cases a chronically diseased appendix (pathologic report) was found at operation. Rosenows states that in his opinion cholecystitis probably occurs when streptococci having an affinity for the gallbladder enter the blood stream. Cholecystitis has frequently been reported as a complication of scarlet fever.2, 9, 10 Here, undoubtedly, streptococci are the exciting cause. Typhoid bacilli may give rise to an infection of the gallbladder, as in the case of the first patient presented. The first report of a series of such cases in children was that by Reid and Montgomery, 11 who recorded 18 cases observed at the Johns Hopkins Hospital prior to 1920, all of which were confirmed at operation. Mohr12 reported one case directly following an attack of paratyphoid fever.

The finding of Lamblia intestinalis in the stool and in the biliary returns of one of our patients is of more than passing interest. Smithies,13 in 1928, reviewed the literature concerning the pathogenicity of Lamblia intestinalis and stated that it has been recognized that under certain circumstances they are decidedly pathogenic. In the lower bowel they may give rise to ulcerative colitis and ileitis. When found in the duodenum they may be pathogenic and, in addition, when found here, they may also be harbored in the gallbladder. Smithies' deductions are based on 5,000 biliary drainages and the finding of Lamblia in massive numbers in the gallbladder when the patients who exhibited the parasites in the biliary returns were subjected to operation. The chronic splenitis and multiple adhesions around the gallbladder, liver, and small intestine in our patient are similar to the conditions found at operation in one of his patients. Golob14 states Lamblia infestation of the gallbladder may simulate acute cholecystitis by obstructing the cystic duct. He reported two such cases. Westphal and Georgi,15 Calder and Rigdon,16 Guerstein and Reydermann.17 and Zelditch and his collaborators4 have all reported cases in which Lamblia were established as the causative agent. The last mentioned authors reported 32 eases of cholecystitis in children, 12 of these having Lamblia in the biliary returns. Lichta18 and Kouznetzoff19 also believe Lamblia are etiologic factors in certain cases of cholecystitis. It should be noted, however, that some authors as Paulson and Andrews20 and Boeck21 believe Lamblia to be nonpathogenic.

The technique of biliary drainage is well known<sup>22</sup> and consists in the introduction of a jutte tube into the duodenum and the injection of a few cubic centimeters of a 25 per cent magnesium sulfate solution

through the tube to promote the flow of bile. The finding of mucus, floccules, leucocytes, parasites, or crystals of cholesterol in the "B" or bladder bile is considered evidence of gallbladder disease. The procedure has been found practical in children and even in infants. In one of our patients it was applied with satisfactory results in diagnosis and treatment, and in another, the diagnosis was made in this manner although operation was later performed. Smithies,13 who employed the method extensively, feels that it is a valuable aid in diagnosis and treatment of gallbladder disease in children. Guerstein and Reydermann<sup>17</sup> have also found it helpful. Zelditch and his collaborators4 have been doing biliary drainages routinely in the out-patient department at Kiew since 1931. They thus have a large series of control cases on which to base their findings in 12 cases of Lamblia infestation. Every patient exhibited abnormal findings in the biliary returns which disappeared after repeated drainages. Coincident with the return of the bile to normal the symptoms were ameliorated.

Oral cholecystography is widely used in the diagnosis of gallbladder disturbances in adults. It is equally applicable in children as demonstrated by Reviglio<sup>23</sup> in 1929. Hamilton, Rich and Bisgard<sup>24</sup> also recommend oral cholecystography in children. In three patients of the present series the diagnosis was made by roentgenogram. In one of these, visualization of the gallbladder did not occur on the two occasions before biliary drainage was begun, but following this the gallbladder filled and emptied normally. In a fourth patient a normal roentgenogram was obtained but the gallbladder was found to be definitely diseased at operation. It has already been stated that Zelditch and his collaborators obtained abnormal roentgenographic findings in all of their patients. Holbrook<sup>2</sup> reported one patient in whose case the gallbladder failed to visualize on two occasions, and a diseased organ was found at operation. Beals' patient7 was diagnosed cholelithiasis by roentgenographic study, and this was also confirmed at operation. Evarts Graham,25 in discussing Beals' paper, stated that at the Children's Hospital in St. Louis about 12 unreported cases of cholecystitis have been seen, in several of which the diagnosis was made by cholecystography. Some of these were confirmed at operation. The others were classified as chronic and not operated upon.

The majority of cases of cholecystitis reported in children have been diagnosed acute appendicitis and it has not been until operation or necropsy that the actual condition has been determined. This is unfortunate, especially in view of the bearing accurate diagnosis has on the subsequent treatment. In Potter's 226 collected cases, 140 had stones, 48 did not, and in 38 there was no statement as to their presence or absence. Since Potter's paper, in over 70 per cent of the cases reported there was cholecystitis without stones. It is the generally accepted practice among experienced surgeons to delay operation in these

patients until the symptoms have subsided and it is, therefore, extremely important to establish the diagnosis, since the treatment of the conditions which might be confused with cholecystitis is quite different.

Among the conditions to be considered in the differential diagnosis are appendicitis, pyelonephritis, perinephric abscess, nephrolithiasis, subdiaphragmatic abscess, diaphragmatic pleurisy, catarrhal jaundice, pneumonia, pericarditis, pancreatitis, peptic ulcer, and duodenitis. The association of acute pancreatitis and cholelithiasis, as in the cases of the third and fourth patients presented, is not infrequent in adults.

#### SUMMARY AND CONCLUSIONS

- 1. Eight cases of cholecystitis in children are reported.
- 2. Cholecystitis is not infrequently the cause of unexplained abdominal pain in children. Often these patients are seen in the outpatient clinic or in office practice and are not subjected to further study. The pain disappears with symptomatic treatment only to recur at variable intervals and the condition is classified as mild gastro-enteritis, indigestion, or subacute appendicitis.
- 3. That Lamblia intestinalis may be an etiologic factor in cholecystitis is mentioned.
- 4. There should be careful study of all children who manifest obscure abdominal pain. The possibility of cholecystitis as one of the causes is emphasized.

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## THE DEVELOPMENTAL HISTORY OF STUTTERING CHILDREN

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THE PROBLEM, THE SOURCE OF MATERIAL, AND THE GENERAL PROCEDURE

E VERY speech clinician has entertained suspicions about the normal physical development of the stuttering child. The clinician realizes that parents seeking an explanation for the disorder very naturally exaggerate the child's deviations from the norm. He is inclined, however, in view of the increasing emphasis on hereditary and biologic factors in stuttering, to listen with some credence to the history of an atypical development. Are the first five years of the stutterer's life entirely normal? Will his developmental record of delivery, birth weight, feeding, walking, and talking compare favorably with that of a child with fluent speech? Does he vary only in one single respect from the non-stutterer?

These questions delineate the problem of the study. Previously, surveys have been made on such developmental criteria as handedness, emotional growth, and social adjustment. We should like to approach the problem by investigating the medical records of these children entered in clinics in early infancy. Through the cooperation of Bobs Roberts, Children's Memorial, and Michael Reese Hospitals, and the Rush Medical Clinic in Chicago we were able to assemble medical historics on 500 stuttering children. The assistance of the Jewish Home Finding Society, the Illinois Institute for Juvenile Research, the Elizabeth McCormick Fund, and the Chicago Orphans Asylum made possible the collection of 500 medical records of nonstuttering children entered routinely for pediatric care.

We were faced at the outset with a very real difficulty: there was a comparatively small number of records which embraced information on all the items in which we were interested. The groups, therefore, vary in size and in certain instances the number is too small to warrant generalization. A most important subject to us, the development of the child's laterality, is not a part of the routine case history outline. The records of the stutterers occasionally embraced information on this point, but the records of the control group rarely mentioned this factor unless the case involved a nervous disorder. No comparison, therefore, can be made on this point.

#### TINDINGS

1. Prenatal Conditions and Delivery. Only distinctly abnormal or pathologic conditions were noted in the record concerning the fetal life of the stutterer. No index of the general condition of the mother during

pregnancy could be secured. An examination of the data on illnesses experienced by the mothers of the two groups, stuttering and control, did not show any material differences except in one particular. In four cases, mothers of stutterers were afflicted with exophthalmic goiter and thyrotoxicosis during pregnancy; there is no mention of this disorder in the records of the control group. The writer recalls that in reading 200 case records of exophthalmic goiter (reported elsewhere), two made mention of the fact that a stutter present in childhood had recurred with the exacerbation of the thyroid condition. In another case history, a case of cretinism treated from infancy, an increase in the dosage of thyroxin suddenly brought on stuttering. Whether the connection between an endocrine dysfunction and stuttering is coincidental or real cannot be determined with the number of cases at hand.

The type of delivery was commented upon by the two groups in practically equal numbers. Reports for 227 stutterers and 232 nonstutterers were available. Table I presents the salient data.

TABLE I
TYPE OF DELIVERY

	STUTTERERS (	(227)	CONTROL (232)
Normal	205		215
Instrument	21	1	19
Prolonged labor	13	[	8
Premature	12	1	13
Breech presentation	6	1	1
Cyanosis	6		ន្ន
Injury to infant	3	1	2
Brain hemorrhage (infant)	2	I	1
Caesarian	1	- 1	4.

The figures show no significant differences between the two groups in type of delivery.

2. Birth Weight. The birth weight of the two groups may be compared although it must be recognized that a greater number was reported for the control group than for the stutterers (Table II).

TABLE II BIRTH WEIGHT

	STUTTERERS (71)	CONTROL (145)
Mean (in lb.)	7.461	7.131
Mode (in 1b.)	7.500	8.000
Median (in lb.)	7.610	7.340
Standard deviation	7.331	6.794
Critical ratio (Diff.)		0.319
S. D.	· I	
diff.		

The critical ratio is low, 0.319, indicating that there are only 59 chances in 100 that the true difference between the groups is greater than zero. Compared with Hardy and Hoefer's study of 406 normal

children, both stuttering and control groups fall below their mean of 8.54, but when compared with Faber's study<sup>2</sup> of 644 normal infants, the mean birth weight of 7.5 pounds which he establishes is matched exactly by the stutterers. The control group again falls below the norm.

3. Feeding. The two groups reported in approximately equal numbers on the type of feeding (Table III).

TABLE III
FEEDING: Type and Period

A. TYPE OF FEEDING	STUTTERERS (189)	CONTROL (201)
Breast Artificial Breast-Artificial	126 52 13	126 51 24
B. PERIOD OF BREAST FEEDING (IN MONTHS)	STUTTERERS (71)	CONTROL (89)
Mean Median Mode Standard deviation Critical ratio	10.634 10.625 12.000 5.600	8.172 9.330 12.000 4.445 3.255

A comparison of the means reveals that the period of breast feeding for the stutterers was 2.5 months longer than for the control group. The critical ratio, 3.255, indicates that there are 100 chances in 100 that there is a true difference greater than zero between the two groups. So many variables, however, enter into the length of the nursing period that it is not possible to give a satisfactory interpretation of the difference. Seasonal considerations, i.e., the prevalent theory that it is unwise to wean children during the summer, economic status, traditional practices of the social group to which the mother belongs, and nationality of the parents are factors which, if fully known, might minimize the differences between the two groups.

4. Walking. Although the largest number in both the stutterers' and control groups began to walk at twelve months, the range among the stutterers is considerably wider (two times). The mean and the median show an appreciable difference between the two groups (Table IV).

TABLE IV
WALKING (AGE IN MONTHS)

STUTTERERS (210)			CONTROL	(226)		====	
No. mode median mean 210 12 13.61 14.8  *Critical ratio: Difference S. D. diff.	S. D. 4.79	No. 226	mode 12	median		S. D.	C. R.* 1.59

If we leave out of consideration the cases of extreme retardation in walking in the stuttering group, because in three of the five cases pathologic conditions interfering with the acquisition of normal control are noted in the record, we still find that an appreciably larger number of stutterers is retarded in learning to walk. The incidence of rickets is greater in the control group than in the stutterers' group, and therefore, it cannot be considered a factor militating against the development of walking in the stutterers.

In the study by Hardy and Hoefer<sup>3</sup> the mean for the total group of 403 children was 13.01 with a standard deviation of 2.93. It will be noted that the nonstutterers in our group are accelerated slightly beyond the mean established by Hardy and Hoefer but that the stuttering group falls definitely below the norm. The average for the control group is slightly higher than the mean established by Terman<sup>4</sup> for 1,000 gifted children (12.98). In comparison with Terman's figures the stutterers are retarded by 1.82 months, the control group by 0.56 months. The critical ratio expressing the difference between the two groups in this study is 1.59, indicating that there are approximately 86 chances in 100 that the true difference is greater than zero.

There is some indication that the stutterers are atypical in the acquisition of motor skills other than speech.

5. Specch. Because the onset of speech is regarded as an excellent sign of normal neural growth, it seems strange that no study previously has been made on the age at which speech begins in the stutterer. We can find no record of such an investigation. Several scholars, however, have given attention to the articulatory and vocal problems of stutterers during nonstuttering speech.

Dr. Elizabeth McDowell,<sup>5</sup> in testing 60 stutterers and a similar number in a control group for speech difficulties other than stuttering, fails "to find a marked disparity between the groups." Mrs. McDowell questions, however, the value of her data because of "certain varying factors in the testing situation brought on by the subjective nature of the scoring."

Dr. Robert West<sup>c</sup> reports that "there are certain demonstrable differences between stutterers and nonstutterers aside from the spasms that occur during speech of the former. The chief of these are: (1) The slowness of diadochokinesis of the articulatory muscles of the stutterer. (2) The lack of inflection of the vocal tone. It may be that the two are related, and that both are caused by muscular spasticity. In slowness of diadochokinesis the stutterers are much like the spastic. The lack of inflection of the stutterers can be noted by the trained ear. After a considerable experience with stutterers, the listener will become aware of the tenseness and inflexibility of the stutterer's vowel sounds. The stutterer's voice shows changes of pitch from word to word, and even from syllable to syllable, but during the utterance of a unit-voiced sound the pitch is inflexible. The normal speaker practically never holds

a vowel level in pitch... His condition in this regard may be thought of as being half way between normal speech and paralytic speech, or as wavering between these two states."

In this study we have collected data on two processes in speech development: (1) the beginning of speech or "first words"; (2) the development of a speech which may be understood by members outside

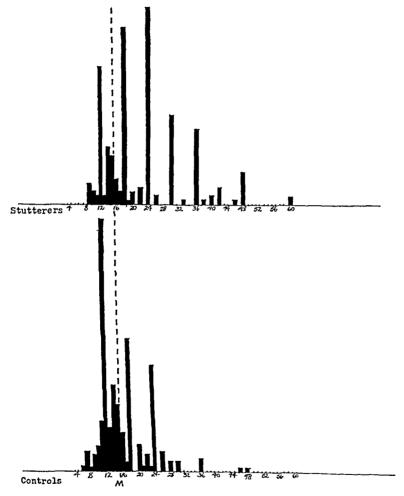


Fig. 1.-Age of onset of speech (in months).

of the immediate family, and hereafter designated as "intelligible speech." Although the figures from other studies are presented, it does not seem wise to rely to any extent upon these figures for valid comparisons because projects not specifically concerned with speech development do not differentiate between the utterance of single words and the development of intelligible, connected speech. The two processes may not be closely linked in time. The work by D. A. McCarthy is

an exception because he is concerned with the language development of the preschool child. McCarthy concludes that "the absence of comprehensible speech in a child of two and one-half years of age should be considered a definitely abnormal condition." Comparative Tables V and VI and Figs. 1 and 2 present the salient data.

TABLE V
FIRST WORDS (AGE IN MONTHS)

	No.	MEDIAN	MODE	MEAN	S. D.	CRITICAL RATIO
Stutterers Control	243 252	18.45 14.25	24 12	23.54 16.12	10.21 6.09	8.49
Hardy-Hoefer <sup>8</sup> Mead <sup>9</sup>	364 50			14.19 15.32	5.39 3.0	

TABLE VI INTELLIGIBLE SPEECH (AGE IN MONTHS)

	NO.	MEDIAN	MODE	MEAN	S. D.	CRITICAL RATIO
Stutterers	140	30.48	30	36.21	14.2	6.854
Control	154	22.38	20	24.18	7.9	0.00*

The findings reveal that the stutterer is definitely retarded in the initiation and development of intelligible speech. The very large critical ratio, 6.854, denotes a reliable difference between the two groups. The ratio indicates that there are 100 chances in 100 that the true difference is greater than zero.

In 39 clinic reports the figures revealing retardation in speech were reinforced by a specific statement that the child was definitely retarded in learning to talk; 38 clinic records noted the presence of infantile perseveration; in 40 cases physicians recorded very indistinct speech; on 17 charts lisping was noted. In many instances the first visit to the clinic was made because the mother was concerned over the child's inability to talk. When speech finally was initiated, it was accompanied by stuttering. This is the typical clinical report corroborated by physician, psychologist, and social worker.

It might be argued that these children represent a group with a low intellectual rating. The average intelligence quotient for 166 stutterers on whom reports were available was 0.992. In the control group there were 161 records containing this information. The mean for this group was 0.976. Both classes are within the range of high normal intelligence and yet there is an appreciable difference between them in onset of speech. The difference cannot be accounted for on the basis of low intelligence. The stutterer evidently begins life with a specific deficiency in the armamentarium necessary for speech.

Discussion of the findings.—On the basis of these records the stutterers differ most significantly from the control group in one respect, the initiation and development of intelligible speech. So many factors enter into the complex picture of stuttering that only a few suggestions may be safely offered to explain the stutterer's retardation. The most valid inference is that the stutterer begins life with a defective armamentarium for speech. This neural arrest some workers now believe to be inherited. Others hold that a prenatal or postnatal toxic invasion of the nervous system has damaged the speech centers and routes. In some cases only infantile perseveration or lisping bears evidence of the damage. In other cases the synergy is so seriously impaired that stut-

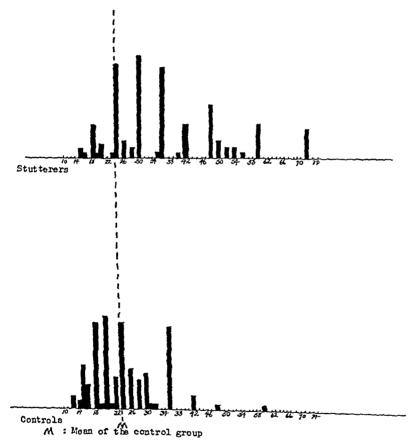


Fig. 2.-Age of development of intelligible speech (in months).

tering results. So the argument runs. The inference of a natively defective armamentarium receives indirect support from Flechsig's tudy of the embryology of the brain. It should be remembered that the White House Conference survey established the fact that "the ratios of stuttering boys to girls above thirty-six months of age vary all the way from 3 over 1 to 8 over 1." Stuttering and maleness evidently are linked. It is interesting, therefore, to note that Karlin and Kennedy, interpreting Flechsig's findings, suggest that the later development of

speech in the male may be caused by a later myelinization of the nerve tracts in the speech pattern. Whether the defect is one of temporary or permanent ablation, or impairment of certain neural centers or pathways, or of a delay in myelinization of the fibers in the speech pattern is not known. In this connection it should be noted that twinning is more frequent in stuttering families<sup>13</sup> and that twins are retarded in their language development.<sup>14</sup>

Those who believe that stuttering is a functional disorder caused by an emotional maladjustment may find this hypothesis, at first glance, a direct contradiction to their views. It should be remembered, however, that emotional disturbances may be the secondary or precipitating cause, not the primary cause of the stuttering. There may be a good many potential stutterers who never break over into stuttering. Their "margins of safety" are wide. If the environment, however, is unsatisfactory, then the child may realize his potentialities for stuttering. The provoking cause, indeed, is the emotional problem but the basic cause may be a natively inferior mechanism for speech.

The same warrant of consistency may be given to those who hold that stuttering is set off by some illness accompanied by a high fever. Endowed by inheritance with an inferior speech mechanism, the potential stutterer may "ride the waves" successfully until a temporary infection or nervous disorder engulfs him. The illness may be of short duration, but the damage may be sufficient to precipitate stuttering.

All in all, whatever theory one accepts, he is forced to recognize the strong possibility of a genic complex in stuttering.

#### CONCLUSIONS

- 1. There was no demonstrable difference between the two groups in the conditions associated with the pregnancy of the mother and delivery.
- 2. The mean birth weight of the stuttering group matched exactly the mean birth weight established by Faber. The critical ratio between the stuttering group and the control group indicated that there were 59 chances in 100 that the real difference between the groups is greater than zero.
- 3. The average length of breast feeding was greater among the stutterers than among the control group. Although the critical ratio points strongly to a true difference, a large number of variables precludes a positive finding.
- 4. The stuttering children were retarded in learning to walk when compared with a similar group of nonstuttering children. The critical ratio indicates that there are 86 chances in 100 that the true difference is greater than zero.

5. The stuttering children showed a serious retardation both in the initiation of speech and in the development of intelligible speech. The very large critical ratios indicate that there are 100 chances in 100 that the true differences are greater than zero.

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## THE EMOTIONAL AND SOCIAL DEVELOPMENT OF GIRLS WITH HEART DISEASE

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FOR the past fifteen years we have had the opportunity to study a large group of girls with rheumatic heart disease. These children were under the observation of one group of observers throughout a greater part of their latter childhood and practically their entire adolescent period. Although the control varied slightly in the two different periods of observation, the personnel that studied the groups was practically identical throughout the entire fifteen years. In addition to the physical problems arising on account of their cardiac disease, the emotional and social development of these children offered an interesting field for study.

Past studies of children with rheumatic heart disease have emphasized primarily the pathology and the prognosis. Although in some institutions attempts were made to establish a satisfactory social adjustment, particularly along vocational lines, none of these was very intensive nor have they been very fully studied.

As our experience with the children who had spent a residential period at the cardiac school increased, we were tremendously impressed by the absence of any instances of real emotional or social difficulties based on the cardiac disease. An estimate of this kind based purely on clinical impressions without substantiation either from specific studies or statistical data, was open to very much doubt. Ordinarily, these children passing from hospital to hospital, out-patient clinic to out-patient clinic diverse in approaches and management techniques, do not offer the necessary continuity for a study in development. It is only under conditions such as we have been able to establish that a continuous record may be kept which offers material of comparative value in these studies.

#### MATERIAL

In order to study the effects of chronic disease and its necessary limitations on the development of children with eardiac disease, a group of 21 girls, who at the present time range between twelve and eighteen years was selected for study. This group was selected from about 130 girls with rheumatic disease, associated with established and persistent cardiac involvement. The method of selection was simply to utilize children

of the older age group that were available. In the period from 1923 to 1928 the group was under our control at the Beth Israel Hospital in the Ambulatory Cardiac Clinic, and from the beginning of 1929 up to the present time, the group has been treated at the Theresa Grotto Residential School for Cardiac Children at Caldwell, N. J. All the children studied have had residential time at the cardiac home. The clinic group consisted of 60 children, 21 of whom are known to be dead, 19 whose records have been lost, and 20 who have been included in the present group for study. Seventy other children have been added since 1929. The mortality of the group that has had a residential period at Theresa Grotto has been 6 out of the 90 children under observation for periods ranging from one to seven years.

The institution is situated in the country about 15 miles from Newark, has adequate grounds, and a building housing 12 children. There is a resident nurse, a resident teacher, and the necessary facilities for the medical study of the group.

In the organization of the personnel, there is only one outstanding difference from the usual plan in institutions for the care of the cardiac child. This group is in the direct charge of a pediatrician with the cardiologist, social workers, psychiatrists, and others acting as consultants. One of the primary results of this arrangement of personnel is that an attempt is made to evaluate and handle not only the physical disability but the mental problems that arise.

The Theresa Grotto is primarily an experimental clinic for the development of procedures and methodology to handle cardiac children to the best advantage. Practically all of the children accepted for study have come from the lower social and economic group. With the great number of children afflicted with rheumatic heart disease, and the small capacity of the institution, a selection was made of those we felt most required the care and help of an organized group.

According to the best available statistics, the incidence of rheumatic heart disease in the schools of our community is approximately 1 per cent. Due to the limited facilities available, we have not as yet been able to develop a service for both sexes, and only girls have been studied.

Rheumatic heart disease, as it manifests itself in childhood and early adolescence is a long drawn-out chronic infection with intermittent periods of exacerbation and remission. The children are admitted to the institution after an attack of cardiac decompensation for which they have been hospitalized, or when found with active signs of rheumatism or rheumatic heart disease.

As will be seen in Table I, the age of the discovery of heart disease varies from two to ten years in the group studied with an average age of seven and one-half years. This is not the age at which the heart disease is acquired, but the age at which, for the first time, the family

had definite knowledge that the child's heart was affected. Table I also shows the number of hospital admissions for decompensation. This is a rather accurate criterion as to the severity of the involvement. It will be noted that the greatest number of decompensations are in cases 6 and 18, one child having 3 and the other 4. These 2 girls are the only ones in our list that have involvement of both the aortic and the mitral valves.

TABLE I

CASE NO.	PRESENT AGE	AGE AT DISCOVERY OF HEART DISEASE	NUMBER OF HOSPITALIZA- TIONS OR THE DECOM- PENSATION	TYPE OF VALVULAR LESION
1	12	7	1	Mitral
2	13	5	1	Mitral
3	13	8	1	Mitral
4	13	8	0	Mitral
5	13	10	0	Mitral
6	13	10	3	Mitral and aortic
7	14	5	0	Mitral
8	14	2	1	Mitral
9	14	6	1	Mitral
10	15	6	1	Mitral
11	15	10	1	Mitral
12	16	7	2	Mitral
13	16	6	0	Mitral
14	16	7	0	Mitral
15	16	5	2	Mitral
16	17	9	0	Mitral
17	17	7	0	Mitral
18	17	9	4	Mitral and aortic
19	17	9	0	Mitral
20	17	6	3	Mitral
21	18	7	1	Mitral
Average		7.5	1.05	

The average length of stay in the institution was about twelve months and the average stay of the children of the group under consideration was fourteen months. As will be seen in Table II, the age of first admission to the Theresa Grotto Home varied from seven to thirteen years. Ordinarily, the child was admitted only once, but in a number of cases 2 or 3 admissions are noted. These readmissions followed acute exacerbations of the original infection while the child was at home, severe enough to demand hospitalization, and later, return to the residential school. The condition of the child on discharge as given in

Table II follows the classification of the American Heart Association. The weight gains also given in this table are an indication frequently not only of the physical improvement of the child, but of the disappearance of emotional factors that influenced the nutrition.

TABLE II

CASE NO.	AGE ON ADMISSION TO THERESA GROTTO	NUMBER OF ADMIS- SIONS	TOTAL STAY (MONTHS)	CONDITION ON DISCHARGE	WEIGHT GAINED (POUNDS)
1	10	1	10	11A*	10
2	7	2	14	1	13
3	- 9	1	13	1	6
4	11	1	11	11A	22
5	10	1	16	1	35
6	12	1	12	11A	13
7	7	1	13	1	8
8	10	1	17	11A	30
9	10	1	11	1	20
10	8	1	23	11A	11
11	11	1	14	1	16
12	11	1	12	1	27
13	9	1	13	1	10
14	9	2	11	11A	12
15	11	2	24	11A	21
16	11	2	10	11A	21
17	9	1	13	1	21
18	12	3	30	11B	35
19	13	1	3	1	10
20	11	3	14	11A	35
21	9	1	10	11A	12

\*Classification: 1, No symptoms; 11A, symptoms on moderate exertion; 11B, symptoms on slight exertion.

Social service surveys have been made on all of the children by the social service units of the various referring hospitals. Psychiatric service and mental hygiene studies have been done by Dr. Fuller of the Graystone Park Unit, Department of Mental Hygiene, State of New Jersey. In addition to the studies by the mental hygiene unit, specific recommendations were made as to the management of the cases admitted. These procedures were carried out in the institution, and the mental hygiene unit further furnished considerable help in readjusting the home conditions of the children in preparation for their return after the stay at Theresa Grotto. No child whose intelligence was below the normal range was accepted into this group. Many of the children were admitted with definite psychic difficulties already established.

#### METHOD OF STUDY

The methods adopted for the study were practical only because of the fact that the children had been under the medical care of the writer for a long period of time. All the cases had been personally controlled by the author for periods of at least four years, and in some cases, as long as twelve years. This long time contact had established both with the child and the family the necessary rapport so that the information desired was readily obtainable and the difficulties ordinarily experienced in establishing confidential contacts were obviated. Records extending back over a period of many years, medical, social, economic and psychiatric, were available from the files.

In every case, at least one primary complete social service survey made at or before the time of the admission of the child to the residential school was available. There also was a complete psychologic and psychiatric survey made immediately after admission. These primary studies have been used to furnish the background for further development, giving a definite point of departure for the comparative studies carried out later. Separate interviews were arranged for the child and the parent. These interviews were planned on the basis of conferences for vocational guidance, and as far as the child knew, there was no record made during the interview.

In addition to the discussion of vocational guidance questions, a rather intensive analysis was attempted as to the general adjustment of the child, particularly in emotional and social fields. These interviews were recorded verbatim by a stenographer in the adjoining room. The summaries of the case histories submitted were made from this interview material. In most cases, only one interview was obtained.

In addition to a study of the material so obtained, two types of objective testing were utilized. "The Adjustment Inventory" of Bell for the classification of the home, health, social, and emotional adjustment, and the "Personality Schedule" of Thurstone were employed. Wherever necessary, further psychiatric studies were made.

The primary difficulty on admission has been the reaction of the child to an overprotective home environment. In our experience it has been impossible to treat these children in their own homes without this factor entering to a very great extent. Frequently this factor enters in the primary examination conducted on admission.

One child admitted to the institution, although fairly well compensated, had not walked within two years of the admission date. In another case, the child gave evidence of so much disturbance at the time of her admission, that the symptomatology might have been ascribed to cerebral damage. Her speech was interfered with, she was extremely distractive, and entirely antisocial. Under observation in the institution, where she had been admitted after the psychiatrist's evaluation of

her mentality as approximately normal, within a year the physical evidence of disorganization disappeared, and although her social and emotional adjustment is not everything that might be desired, it is at least within the accepted standards for normally mental children.

#### CASE HISTORIES

We will first present a résumé of the case histories as obtained from the interviews cited above. In addition to this interview material there has been incorporated into these summaries information concerning the child and the family obtained from other children and from the social workers who were in charge of these cases. All of these case summaries are divided into two parts. The first is a description of the status of the child on or about the time of its primary admission to this group. The second is the status, as closely as we have been able to determine, of the child at the present time. It will be noted that the interval of time between these summaries varies from two to eleven years.

#### SUMMARIES OF CASES

Case 1.—At ten years. The patient is a small Jewish girl. The heart disease was first recognized at seven years and she was hospitalized for decompensation for ten months at that time, at Beth Israel Hospital. The social worker states, "Due to the intelligence of the parents, the child should straighten out." The psychiatrist reports, "No mental hygiene problem, very superior intelligence." At twelve years. The father is a university graduate, admitted to the bar in

New Jersey but has never practiced. He was a small manufacturer until the depression, after which the family, although not on official relief, was supported to a very great extent by relatives. The mother is of the aggressive type, extremely disappointed in her present status. The illness of the child has been a matter of grave concern to both parents, particularly because some recommendations that were made were financially impractical. The child is extremely bright, highly successful scholastically with an adult comprehension of the difficulties that exist. One of the major factors in the lack of friends and associates has been the feeling of social misplacement. Although only twelve years old, she has established a definite boy and girl friendship that is probably thoroughly dramatized along the lines of the romantic literature of the period which she reads. In these daydreams she apparently is finding adequate satisfaction for her lack of personal social contacts. Many of her reactions are old for her age, and her reserve in the interview was very noticeable. This was not a shyness based on inadequacy but rather the well-poised control of a well-developed child. This child's emotional difficulties are related to an unsatisfactory home and economic situation rather than to her physical condition. She has never utilized her physical handicap as a method of obtaining desired ends.

CASE 2.—At seven years. The first knowledge of heart disease in this child was at the age of five years. She was decompensated at six years and hospitalized four months. On admission, the psychiatrist reported, "High average intelligence, attention-getting mechanisms on a basis of the cardiac pathology." Social worker's report, "All children in the family present potential behavior problems due to the lack of discipline. All the children complain about favoritism to this child on account of her physical condition."

At three years. This patient is an Italian girl, living in a mixed Italian and colored neighborhood. She is greatly restricted by the parents. The element of over-

protectiveness in this situation is counteracted by the fact that this attitude is a customary and accepted attitude in their own social group. This child is attractive and well developed for her age. She was thoroughly at home and well poised, and spoke readily without he-station. There are no difficulties at the present time with the other children in the family and there is no attempt to utilize the cardiac pathology to obtain desired satisfaction. Socially, she is very well adjusted.

CASE 3.—.1t nine years. The child is definitely below average in physical development. Her intelligence is of low average grade and she presents no specific mental hygiene problem. There is very little attempt at attention getting on the basis of her cardiac pathology.

At thirteen years. The case presents a thirteen year old Italian girl, well developed, of low average intelligence. She is one of 6 children in a first generation Italian family. The restrictions of this social group are evident but accepted. She has congenital syphilis and is receiving treatment. She is a rather self-contained child and resents anything that reminds her of her physical disability. She was unwilling to come to the interview, but after she arrived, cooperated fairly well. Her interests and accomplishments are within the range of her ability. Her social adjustment is fairly good. Apparently in some of her social relationships, i.e., her ability to escape from routine gymnasium work in schools, and the fact that some of her friends are somewhat careful as to her feelings concerning her heart condition, advantage is taken by the child of her cardiac condition. In spite of this acceptance and the utilization of her heart lesion, within very marked limitations, she seems to have no other reactions to her handicap.

CASE 4—1t eleven years. In this girl the first heart involvement was known at eight years. The social service worker reports, "Child is nervous and irritable, sleeps poorly, goes to bed rather late, is rather difficult to manage, cries easily, becomes sullen." Psychiatrist's estimation, "Average intelligence, easily distracted and not cooperative." Home conditions very poor, economic conditions very bad.

At thirteen years. The patient is an average Italian girl, well developed, with an extremely pleasant manner, a ready smile, a rapid answer. She is above her group both in intelligence and poise. She seems to have no difficulties of any kind in her social adjustment.

CASE 5.—At ten years. The child was admitted from an orphanage. She was a normally intelligent child with no special mental hygiene problems.

At thirteen years. The girl is well developed, about one year behind in scholastic work due to lack of schooling. She lacks the poise and assurance that many of the girls of this group have, and exhibits a certain amount of shyness. She is having a rather trying time; her mother died four years ago, her father has remarried, and the child says the stepmother is extremely jealous of the children. Her emotional problems, although very real and probably interfering to a certain extent with her social adjustment, are not on the basis of the heart disease but rather on the basis of the home situation.

Case 6—At tuche years. This twelve year old girl has been very sick, and in the last three years has spent most of her time in hospitals. There is no mental hygiene problem except that due to prolonged invalidism.

At thirteen years. The child is poorly developed. She is apparently somewhat shy in ordinary contacts, but probably more at home in the interview due to our longtime contact. She shows no evidence of any emotional blockage due to her heart condition except as she says that under certain conditions she has a rapid heart beat which she believes to be visible. When this occurs, she is shy, nervous, and attempts to withdraw from public appearances. However, this condition is not frequent, and in spite of it, she is secretary of her class, sings solo parts in the

glee club organization, and is chairman of the current events club in school. There are, however, factors in this child's home that may produce difficulties in the future.

CASE 7.—At seven years. The first knowledge of heart disease in this child was at five years. The psychiatrist reports, "Inferior intelligence, marked inferiority feelings, shy and retiring, probably on a basis of cardiac condition."

At fifteen years. The patient is a well-developed Polish girl of a low normal group intellectually, who is having many real difficulties in adjustment. Although perfectly at home in the interview, her general reactions are those of extreme shyness and inability to make friends. Her inferiority feelings have been exaggerated by her low school placement which to a very great extent, has not been due to her illness but to her lack of intellectual capacity. She explains her inability to make friends as based on a lack of desire to mix with Italian children socially. This probably is also a reaction to her own feeling of inferiority. Although this child presents many problems, there is no reason from the interview to believe that any of these problems has been aggravated by her physical condition, but rather to believe that the group training to which she has been subjected at the institution may have helped her to make some classroom adjustments that otherwise could not have been possible.

Case 8.—At ten years. The first knowledge of heart disease was at two years. She was admitted to Baby's Hospital at this time with pneumonia and empyema. She had recurrent attacks of carditis in January or February in each year for the next four or five years. At no time has there been any decompensation. This child on admission presented evidence of psychic disturbance on the basis of an overprotective home environment.

At fifteen years. Economic conditions in this home were unbelievably bad. The father was killed two and one-half years previously, and there has been extreme poverty since that time. The child is very sensitive to home conditions, to her lack of clothing, and to the poverty in which she is forced to live. The mother is totally incompetent, sick, and slovenly. This child has many personality difficulties, but all of them are based on home conditions and not on her heart lesion.

CASE 9.—At ten years. The first knowledge of heart disease was at six years. She had numerous attacks of chorea. The psychiatrist states, "Average intelligence, guidance problem on account of attention-getting mechanism. Utilizes cardiac disability as a method for obtaining of attention." She was at Caldwell eleven months, having been admitted as Class 11A. She gained 20 pounds in one year. The social service worker reports on admission, "Two years retarded at school, and annoys children in class by actions. One teacher said she was always getting into trouble."

At fifteen years. The patient is a Jewish girl, large for her age, rather attractive looking. Low average intelligence and seventh grade school work is about the limit of her mental ability. She is having considerable difficulty in some of her studies, and is rather embarrassed by the lack of progress in school. She is interested in dramatics and apparently has very little self-consciousness about public appearances. Her social development is perfectly normal. There is no evidence of any social or emotional difficulty on account of her heart disease. When questioned regarding her school standing, she deliberately gave the information that she was one year ahead of her actual grade. She is taking dramatic lessons and is planning for the future on the stage or in radio.

Case 10.—At eight years. With this child the first knowledge of heart disease was at six years. On two separate psychiatric examinations, the child was rated as of low average intelligence, and the second time as a definitely inferior child. She was admitted to Caldwell at eight years and stayed twenty-three months.

During this period she gained 11 pounds. She was rated in class 11B. She had one hospital admission for decompensation. The psychiatrist's examination showed a low average intelligence, and the psychiatrist reports, "I have obtained a rating that I think is entirely unfair. In a test where the child was permitted to work on her own she seemed to show about average intelligence. She seems to go into some sort of a panic when you try to directly ask her a question." There is no direct evidence in this case of any abnormal utilization of her cardiac disability.

At fifteen years. The patient is a fifteen-year-old girl of definitely low mental ability. The younger brother is a low grade moron. The family has been on relief for two years. She takes no active leadership in any activities in school, and presents no problem as long as she is in a protected environment. Her heart disease probably furnishes her with the readily available explanation for all of her inadequacies, and is frequently utilized as such.

CASE 11.—At cleven years. The first knowledge of heart disease was at ten years. This child has normal intelligence and presents no particular mental hygiene problem.

At fifteen years. The patient is a well-developed, stolid appearing, Jewish girl with a ready mind and a fair amount of ability. She has a persistent educational drive probably greater than her actual mental attainment. She is in a difficult social position due to religious factors which seem at the present time to be the basis of most of her disturbances. Her attitude toward her heart disease is one of absolute acceptance, with a tendency to ignore all of its implications and possibilities.

CASE 12.—At eleven years. The first knowledge of heart disease in the patient was at the age of seven years. The child was very difficult and badly adjusted both at home and in school. The psychiatrist reports, "Superior intelligence, bad home environment, many difficulties on basis of attention-getting mechanism on her heart disease." She stayed at Caldwell one year. She has had two previous attacks of cardiac decompensation.

At sixteen years. The girl is in attendance at high school and is doing reasonably well. She is having a great deal of difficulty in her social adjustment on a basis of a feeling of inferiority about which she definitely complains. She attributes this to the fact that she is not able to dress well or to have the things in her home that most other children have. She shows a definite shyness. Whether this is truly on the basis of the financial position of the family or whether it is due to other causes has not been determined. There is no attempt at the present time to use her cardiac pathology as an escape mechanism. She does better on the personality test than would be expected by the interview.

CASE 13.—At eleven years. The first knowledge of heart disease was at six years. There was no hospitalization for decompensation. The psychiatrist reports, "Shows average intelligence with no special mental hygiene problem." She was thirteen months at Caldwell and gained 10 pounds.

It sixteen years. The patient is a rather small, normally developed, Jewish girl with an extremely vivacious and happy personality. She is particularly interested at the present time in high school athletics and athletes. She apparently has a full social life, and in spite of her heart condition takes part in basketball, as a member of an outside team. The child gives the impression of an exceptionally well-adjusted adolescent girl who is having a very good time in everything she does, and to whom the heart lesion means absolutely nothing.

CASE 11.—It nine years. The child shows average intelligence but there is definitely bad environment. The psychiatrist reports, "Utilizes sickness as an attention getting mechanism." The father deserted this family when the child was

six months old. The older daughters are now married but for a long time were definite social problems. The child, when she first came under observation at seven years, had very definite adjustment problems both on the basis of the difficult home environment and the possession of sexual knowledge and interest far beyond her age.

At sixteen years. The child is well poised and has made a successful school adjustment. She is apparently developing along perfectly normal lines, and the extra protection that her lesion has given her has very probably been a saving characteristic in the life of this child. Her interests are normal for her age and she shows normal social development. She plans to be a dental assistant. This is possibly due to a long continued hospital contact, but her choice is well reasoned and intelligent, and there is no reason to believe she will not be able to carry it out to a fairly successful conclusion.

Case 15.—At eleven years. The first knowledge of heart disease was at five years. For the last four years before her admission to Caldwell, this child had been completely hospitalized. Her mental hygiene problems are those of long-continued hospitalization.

At sixteen years. The patient is a sixteen-year-old American girl of German parentage, the fourth of five children in a normal middle-class family. They have never been on relief as the father is a skilled laborer and has worked fairly steadily even through the depression. She is very large and has some difficulties due to the fact, as she says, that she is one of the two largest children in the school. She has a definite reading disability even beyond what might be expected with her slightly below average mentality. Her ratings on most of the tests probably are lower than is actually justifiable on account of this reading disability. She is not exceptionally shy, although somewhat retiring, and has only a few close friends. Her heterosexual contacts have not been established and although she is sixteen years old, her reactions are decidedly below her chronologic age. She has the advantage of a home background that is relatively free from overemphasis either on her physical condition or her mental handicaps. She is the only child in the group that is definitely left-handed. On the whole, she has made a reasonable adjustment to her cardiac condition. It is noticeable that the release from gymnasium which she has obtained on the basis of her condition is looked upon as a decided advantage and not a handicap.

Case 16.—At eleven years. This patient was referred from the child Guidance Clinic. The social worker states, "Rather dull, low average type, stumbles over her words while talking." Psychiatrist reports, "Child guidance problem, inferior intelligence, organic handicap."

At sixteen years. The patient is an extremely attractive, vivacious, sixteen-year-old-girl of Italian parentage. She is working in a factory and has made exceptionally good adjustment socially and in her work. She is extremely interested in boys in general, and at the present time, one in particular. Her attitudes on sexual relationships are typical and normal of the age group. Her main resentment at home is against the restrictions of the old-fashioned Italian family which are in this case fairly rigid. However, they are fairly well accepted since they are common in the social group in which she lives. She completely suppresses all knowledge of her cardiac lesion and its possible limitations. The extremely bad showing on the personality test is probably based on her history rather than her actual existing conditions.

Case 17.—At eight years. The psychiatrist reports, "Normal intelligence, no special mental hygiene problem." The child, however, is somewhat immature for her age and shows the effect of an overprotective home environment.

At seventeen years. The patient is a well-developed girl, mixed German and Irish extraction, not quite as self-possessed and poised as most of the children in

this group. She has been fairly successful scholastically and at the present time is working. Her ambitions and plans for the future are practical. Socially, she seems to be making a normal adjustment for her age and social group, and there seem to be no difficulties on the basis of her cardiac pathology.

CASE 18.—At tuche years. The first knowledge of heart disease in this girl was at nine years. She was admitted to the hospital in December, 1929, and stayed there for three years. From September 1931 to January 1935, this child alternated between the hospital and the convalescent home at Caldwell. She has had numerous attacks of cardiac decompensation. Since January 1935, she has been at home. The child has a mitral and aortic lesion and blood pressure 190 over 0. She is of superior intelligence, but shows the characteristic dependencies of a child who practically has been brought up in a hospital. The psychiatrist made no special recommendations because prognosis was so bad that it was not thought worth while to attempt any special treatment.

At seventeen years. The girl is well-developed, especially pretty, with red hair and fair skin. She was well poised and very cooperative during the interview. Although a very attractive looking youngster, to the trained eye she shows the marked pulsations of nortic insufficiency. In spite of a very difficult home situation, this child seems to be well adjusted both socially and emotionally.

Case 19.—It thirteen years. The first knowledge of heart disease in this patient was at nine years. There was no history of decompensation. There had been three attacks of rheumatic fever with arthritis and one attack of chorea. The patient stayed at Caldwell three months and gained 10 pounds. This child was admitted on recommendation of the Child Guidance Clinic with the complaint that the child was absolutely unmanageable at home.

It secenteen years. She is an extremely attractive Italian girl, well poised and physically well developed. She is working at the present time in a factory but is anxious to become a dress designer, the handicap being purely financial. She is of better than average mentality and seems extremely well adjusted. The problem of her home is primarily that of a young girl in an Italian family with usual restrictions. It does not seem that there is any special attention paid to her heart condition either by her family or herself. She lives a perfectly normal life, has normal desires and realizations. Her social development is better than average.

CASE 20.—.1t cleicn years. The first knowledge of heart disease was at six years. The child was hospitalized for decompensation at seven years. She remained in the hospital five months. At nine years she was again hospitalized, remaining six months. She stayed at Caldwell fourteen months and gained 35 pounds. Previous to admission, this child had spent almost the entire last five years in hospitals. The psychiatrist reports, "Average intelligence with no special mental hygiene problem." The home situation was totally inadequate, her mother having died when the child was about five years of age. The father remarried and died within two years.

At scienteen years. The home conditions of this child are so had that she was discharged from the institution to a foster home. In the foster home she has made a very desirable social adjustment. She seems to have no real emotional difficulties. This child is a very submissive type of youngster, and has accepted her heart disease without any special disturbance.

CASE 21.—. It eleven years. The first knowledge of heart disease was at seven years. This child showed all the reactions typical of overprotection and was infantile even beyond what would be expected with a limited intelligence. Psychiatrist reports. "A low average intelligence."

At eighteen years. The patient is a stolid, overdressed, oversophisticated girl, a rather dull normal with only seventh grade schooling. She has made a fairly successful adjustment, making up for her intellectual deficiencies by a fairly attractive physique and a willingness and desire for social contacts. Her comprehension of her disability or own shortcomings is practically nil.

In addition to the data presented above in the summaries of the case histories, two methods of objective testing were employed. These tests were selected because they appeared to have been properly standardized and could give us some method of establishing comparative ratings. Furthermore, they were fairly easy to apply in the age group with which we were dealing. The "Bell Inventory" with its divisions into home, health, social, and emotional adjustment, seemed to be particularly well planned for this work.

TABLE III

RATING ON BELL ADJUSTMENT INVENTORY

CASE NO.	AGE	номе	НЕАІ/ТН	SOCIAL	EMOTIONAL
1	12	5	6	10	20
$\tilde{2}$	13	Ō	7	17	14
2 3	13	13	5	13	10
4					
4 5	13	0	9	8	2
6	13	10	4	13	
7	14	27	12	18	4 15
8	14	9	14	18	12
9	14	9	8	5	6
10	15	6	11	20	10
11	15	16	11	11	12
12	16	0	4	14	2
13	16	6 8	6	6	4
14	16	8	20	15	11
15	16	2	6	16	3
16	16	17	19	14	27
17		ł	\		
18	17	5	14	16	<u>-</u> 1
19	17	14	5	8	17
20	17	3	7	10	3
21	18	2	5	4	4

#### BELL INVENTORY TESTING

As will be seen in Table III, the "Bell Inventory" classification of the home adjustment shows a fairly average distribution. The distribution, if anything, is a little better than would be expected in a normal group from the same economic class that these patients represent. In the section on health inventory, this distribution, representing the personality health factors, shows in 14 out of 19 cases, average or better than average ratings and indicates only a slight increase in health consciousness above the figures for a normal group of this age.

Apparently, from the standpoint of the effect of the chronic illness from which these children suffer on their personalities, this method, as employed, does not indicate any evidence of increasing personality difficulties on the basis of the cardiac disease. The social rating on the Bell scale is of extreme interest. We are dealing with a group of children with a long-continued disabling condition whose social ratings according to the Bell scale are definitely above average. Of the 21 children under consideration, no single child has fallen below the average rating, and 8 out of the 21 show either good or excellent ratings. On the emotional adjustment, 17 out of the 19 children were average or better. Only 1 case, No. 16, rated very unsatisfactory. This rating, confirmed by the Thurstone Personality Schedule, can be very readily

TABLE IV

CLASSIFICATION OF RATINGS ON THE BELL INVENTORY

(CLASSIFICATION NUMBERS)

	Home	
Rating 0-2	Group Excellent	No. of Cases 5 3 7 3 1
35	Good	<u>ಕ</u>
613	Average	7
14-20	Unsatisfactory	<u>ئ</u>
20—over	Very unsatisfactory	7
	Health	
Eating	Group	No. of Cases
01	Excellent	1
2-4	Good	$ar{f 2}$
511	Average	1 2 11
1216	Unsatisfactory	3 2
16-over	Very unsatisfactory	2
	Social	
Rating	Group	No. of Cases
04	Excellent	ī
510	Good	$\frac{1}{7}$
1121	Average	11
22-30	Unsatisfactory	0
30-over	Very unsatisfactory	0
	Emotional	
Rating	Group	No. of Cases
03	Excellent	3
4—S	Good	3 6 8 1
918	Average	8
18-24	Unsatisfactory	1
24—over	Very unsatisfactory	1
	•	

explained if the past history of this child is understood and evaluated. The writer and his associates felt during the examinations that this rating was rather an expression of historical facts than of present emotional difficulties.

#### THURSTONE PERSONALITY TESTS

The Thurstone Personality Schedule which was the other objective test selected for this group shows a similar high distribution. Fifteen out of 19 children show average or better. Only 3 are emotionally maladjusted, and only one Case, No. 16, to which reference was made above, shows the need of any special therapy on the test.

From the mass of material gathered at the interviews, we have attempted to tabulate some of the data in a form that would make it easier

TABLE V
RATING ON THURSTONE PERSONALITY SCHEDULE

CASE NO.	AGE	RATING	CASE NO.	AGE	RATING
1	12	57	12	16	22
2	13	43	13	16	20
3	13	37	14	16	52
4-	13	none	15	16	24
5	13	24	16	17	98
6	13	24	17	17	none
7	14	60	18	17	28
8	14	76	19	17	54
9	14	22	20	17	27
10	15	45	21	18	15
11	15	44			1

TABLE VI

### CLASSIFICATION OF RATINGS ON THURSTONE

#### PERSONALITY SCHEDULE

The division into groups according to Thurstone is as follows:

Ratings	Group	No. of cases
0-14	Exceptionally well adjusted	0
1529	Well adjusted	9
3059	Average	6
6079	Emotionally maladjusted	3
80—over	Psychiatric admission note	1

to visualize the actual development of these children. One of the factors that interested us was the attitude of the child to her heart condition and the question of whether or not there was any direct relationship between the resentment felt at the disability and the physical extent of the disability. A study of Table VII shows that apparently this

TABLE VII

CASE NO.	DEGREE OF	ADMITTED	RESENTED	CASE NO.	DEGREE OF DISABILITY	ADMITTED	RESENTED
1 2 3 4 5 6 7 8 9	1 1 2 1 1 1 1 1 1 1 1 1	yes no yes no yes no no yes no yes	no n	12 13 14 15 16 17 18 19 20 21	1 2 1 1 2 1 2 1 2 1	no yes no no no yes yes yes yes yes yes	no no no no no no no no

is not true. In determining the degree of disability for the purpose of this table, Class 1 represents children who were able to take part in practically all normal activities and had, therefore, very little restriction in their ordinary contacts. Those classified as Class 2 were children for whom it was impossible to carry out the normal play activities of this age group with anything like the efficiency that the average youngster shows. It will be noted that all the children in Class 2 admit definite disability and that very many of the children in Class 1 also admit their cardiac disability. There were 9 cases out of the 21 that refused to admit any disability at all. It was impossible to elicit from any of the children any statement that would tend to show an attitude of resentfulness toward their disability.

One other table has been added which presents an interesting view of the reactions of these children to their heart condition. All of these children are excused from attendance in gymnasium in the school. It will be noted that in Case 15 the child tells her classmates, with evi-

TABLE VIII
GYMNASIUM EXCUSES

2. Does not tell
3. Tells reason
4. Tells reason
5. Tells with pride
6. Does not têll
7. Does not tell
8. Tells reason
9. Does not tell
0. Tells reason
1. Tells reason

dences of pride, that she does not have to take gymnasium because she has a heart lesion. Apparently to this child, this condition seemed to place her in a favored class. Out of the 21 cases studied, case No. 1 being in a cardiac class, of course would find it impossible to hide the reason for her gymnasium excuse. Of the others, only 5 out of the 20 have any reluctance at all about telling their playfellows the reason for their excuses from gymnasium. All the other children apparently admit the reason without any special feeling of incompetency.

The characteristic statement made by these children in this connection is: "Oh, yes, I am excused from gymnasium on account of my heart, but very many of my friends are excused from gymnasium. Some of them have appendicitis, and some of them have other conditions."

There does not seem to be any special feeling of disability connected with gymnasium excuses in the public schools in our city.

#### SOCIAL ACTIVITIES

As another check on the social development of these youngsters, it was interesting to see how many of them actually took an active part in the social life of the school and their community. Of course, as small

a group as this does not lend itself to statistical analysis, but even a cursory glance over Table IX which shows the activities of these children in leadership in schools, clubs, etc., furnishes a very interesting

TABLE IX
CLUB ACTIVITIES

- 1. 0 2. President of school council 3. 0 4. 0
- 6. Secretary of current events7. Secretary of social club
- 8. 0

5. 0

- 9. Cheerleader, chairman of program and entertainment committees
- 10. Treasurer of social club, President of dramatic club, solo singer
- 11. 0
- 12. 0
- 13. Editor of school paper
- 14. Glee club, solo parts, class secretary, chairman current events
- 16. Vice president, treasurer social club
- 17. President social club
- 18. Class president
- 19. 0
- 20. Secretary social club
- 21. President social club

commentary on their social development. Certainly, this group as shown by the table is more active in the social life available than the average child could possibly be.

In Table X, an effort was made to find out what the reaction of this group was to public appearances. The assumption was made that if a child suffered from a definite feeling of inferiority she would be very unlikely in the ordinary schools of the community to attempt performance in public. Nine out of the 19 children examined definitely perform in public, and this certainly may be accepted as evidence of the lack of any general tendency in the group to withdraw. We have classified this reaction to public appearances according to 4 groups.

TABLE X
PUBLIC APPEARANCES

CASE NO.	CLASSIFICATION NO.*	CASE NO.	CLASSIFICATION NO.
1 2	3	11 12	1 4
4 5	2 1	13 14	3
6 7	4 3	15 16 17	3 2
8 9	3 3	18 19	3
10	4	20	2 2

<sup>\*1,</sup> Dislikes; 2, likes but bashful; 3, performs; 4, indifferent.

1. The child who definitely dislikes to make a public appearance. 2. The child who would like to make the appearance but feels a certain sense of insecurity and bashfulness. 3. The child who actually performs in public. 4. The child who is entirely indifferent, neither desiring to perform in public nor being especially distressed by the necessity when it arises.

As will be seen in Table X, only 5 of these children were classified as group 1 definitely showing some withdrawal tendency; 4 as group 2 which may be taken as indicating children in whom some inferiority complex exists; 9 as Group 3 children who are actually making some type of public appearance; and 3 as Group 4 children who although occasionally making a public appearance, are not particularly interested in this sort of thing. Although the group is small, the distribution is extreme enough to make one feel that at least for the group as a whole there has been no definite disturbance that would interfere with their making public appearances.

One other very interesting observation has been that where a child suffers from a serious ailment, there is usually a tendency on the part of the family to overcompensate for it. When there are other children in the family, this very frequently gives rise to a very unpleasant and sometimes a serious situation. Sibling rivalry is very hard to ascertain in an interview, but where the entire family is known, as is the case with the group under consideration, very frequently evidences of sibling rivalry may be obtained from the other children. Table XI gives a classification of these cases which we believe to be fairly accurate.

CLASSIFICATION CLASSIFICATION CASE NO. CASE NO. NO.\* NO.  $\overline{13}$ 5 6 2, disbelieves other s child's illness 

TABLE XI SIBLING RIVALRY

Only 3 of these children show excessive rivalry at the present time. This was a very definite part of the attitude of very many of these children when first seen. In Case No. 20, the sibling rivalry is so intense that although the other child really is seriously ill, this child is unwilling to admit the possibility of any real illness.

<sup>&#</sup>x27;X, no sibling; 1, normal; 2, excessive; 0, nothing.

#### VOCATIONAL INTERESTS

Most of these children are approaching, or have already entered into the age group where definite vocational guidance is necessary. A tabulation was made of the vocational interests and choices in Table XII.

On the whole, the vocational choice is very similar to that of any group of girls of like age in the economic and social status from which these children were drawn. There is, however, a preponderance of serv-

TABLE XII
VOCATIONAL CHOICE

1. 0	11. 0
2. 0	12. Nurse
3. 0	13. Secretary
4. Secretary	14. Secretary
5. Secretary	15. 0
6. Nurse	16. Nurse, dietitian
7. Dress designing	17. Secretary
8. Factory hand	18. Nurse
9. Commercial art	19. 0
10. Radio acting	20. Nurse, technician
zor zmaro uoving	21. Factory hand

ice vocational choices; nurses, dietitians, and technicians. On further questioning most of the girls seem to have been influenced primarily by the fact that for so great a part of their lives, they have been in contact with hospitals and hospital personnel. It is only natural, therefore, to expect that many of them will set up as their own ideal some individual within the group with which they have been in close association.

Some very interesting information was obtained on the problem of heterosexual contacts. These girls ranging from twelve to eighteen years are in an age group where the development of heterosexual interests is an extremely important factor in evaluating their general development. Information of this type was obtained with unusual facility because the interviewer had stood for many years in loco parentis to the children. As a matter of fact, his professional prestige and their own long history of dependencies made them especially confiding. have attempted in Table XIII to classify these contacts in five groups. Group 1 where heterosexual contacts are not desired were girls that exhibited the ordinary attitudes of girls about nine or ten years of age. Some of the characteristic statements in this class were, "I don't like any boys," or "Boys in my class are fresh, when the teacher talks to them, they think they are smart." "Parties are better when there are no boys there, because they make too much noise." "We are much better off without boys. Our science teacher thinks so." "I don't like to go out with boys yet." "I don't think they notice your clothes but the girls do."

CASE 2 ĩ

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	HETEROSEXUAL CONTACTS							
N0.	PRESENT	AGE	CLASSIFICATION NO.*	CASE NO.	PRESENT .	\GE	CLASSIFICATION NO.*	
	12		4	11	15		2	
	13		1	12	16		1	
	13		1	13	16		4	
	13		3	14	16		4	
	13		1	15	16	1	3	
	13		$\bar{2}$	16	17		5	
	14		ī	17	17		4	
	1 14		$\bar{3}$	18	17		4	
	14		4	19	17	1	4	
	15		ī	20	17		3	

18

TABLE XIII

In Group 2, we took for classification what is apparently a very frequent attitude in early adolescence. The type of answer that was obtained in the interview was something along these lines: "I don't care for boys very much." "I don't know very many boys, sometimes I walk to school with a boy." "I feel sort of self-conscious with boys at a party. I guess I am bashful. I guess they know it too. tease me and say I am bashful."

In the third group we have attempted to include those who have accepted and established definite boy and girl relationships, but still at the same time are reticent when questioned concerning these relationships. Ordinarily, this makes up a very large group, but in the interviews as conducted, there are only 4 cases that fall definitely into this classification, and from whom it was impossible to get any definite statement as to their attitude toward boys. Characteristic statements in this group are such as: "I don't think boys spoil a party, but I don't care whether they are there or not." "I know some boys but I don't go to their houses." "My girl friend has a boy friend but I don't have any special boy friend." "Sometimes you have more fun when boys are there, and sometimes more fun with girls."

Group 4 is the largest group among the older girls in the series. Here their very definite interest in boys is manifest, but it is an interest in groups of boys rather than single individuals. Most of these children state that they like mixed parties rather than parties with girls alone, and they like to go out in crowds with boys and girls. all energetically deny interest in any special boy, and apparently this is true as most of the contacts seem to be those of groups of girls with groups of boys rather than individual contacts.

There is really only one case in this whole series classified as 5, the adult type of relationship where a definite boy and girl friendship has been established with the idea of a future marriage. This type of relationship of course, is completely out of the range of adolescence.

<sup>1,</sup> Not desired; 2, bashful but desired; 3, accepted but reticent; 4, frank; 5, adult.

### INFLUENCE OF PHYSICAL DISABILITY

There has been a large amount of investigation done on the effect on children of the presence of visible physical deformities. Common experience has shown that the sufferer from infantile paralysis with the lame leg; the child with a harelip; the child with a noticeable birth mark, have all tended toward a psychic disturbance based on the physical deformity itself. Whether the knowledge in the child of the extent of the physical deformity, or the reaction of the community to this deformity is a primary factor in these psychic disturbances has not been evaluated. Occar M. Sullivan³ says:

"It is quite essential that even in the earliest years the right principles for dealing with the handicapped condition as it affects the child shall be understood by the parents and by the others around him. Otherwise in the pre-school period, or in the out-of-school time, the child may receive such a conditioning that he can never face the world adequately and play a self-contained individual's part in it..."

In spite of the fact that this writer advises the development of compensatory accomplishments, he states in another part of the same paper this recommendation:

"A second important recommendation of the mental hygiene advisers is so to train handicapped children that they avoid the escape habit. They should know from the beginning that they will have to face realities. Pity and coddling have no place in the treatment of the handicapped child . . . . "

It is worthy of note that a physical deformity in itself is not always the cause of psychic disturbance. The saber scar of the dueling student in a German university has a very close resemblance to the facial deformity following an automobile accident; but one would never compare the feeling of pride that accompanies one with the distress and the desire to withdraw that is the result of the other. Similarly, in our eyes, the harelip is no greater deformity than the large plate lips of the Ubangi maiden which in her social group is a sign of great beauty. The reaction of the social group to these voluntarily inflicted deformities always contains within it this element. How true this is is still further brought out by the general concept in poetry and literature that a deformed body contains a deformed mind; that the hunchback and dwarf while jesters for a court had always to be reckoned with as treacherous, antisocial, and destructive. This viewpoint we believe is sometimes not fully appreciated. R. A. Jefferson<sup>4</sup> states:

"... Whereas the visibility of the one type defies secrecy and promotes a compensatory psychobiological striving while the world makes allowances, the hiddenness of the latter, with the secrecy and shame which so frequently accompanies, makes of social adaptation a doubly difficult task...."

We do not believe that this is true, because in our experience, the social adaptability of these children when proper mental hygiene pro-

cedures has been instituted, is very much greater than that which may be hoped for in any group of visibly physically deformed children. In support of this contention, Brenton M. Hamil,<sup>5</sup> states as follows:

" . . . Much is continually being said about the inferiority feelings which develop in an individual as a direct expression of his feelings of incapacity because of a physical abnormality. This may be true in rationalizing adults. . . . The abnormality in itself is not the greatest handicap. The emotional conflicts which result because of parental or social attitudes regarding these abnormalities are of most importance. A person who is constantly hearing some kind of reference to his abnormality or who is constantly having things done for him which he is capable of doing with some degree of efficiency himself, will either show a quite natural reaction, revolt, or he will take advantage of the situation to get unhealthy recognition because of his physical handicap. Constant attention to a handicap, whether it be in the form of nicknames relating to it, or whether it be in the form of sympathy or special privileges because of it, will usually become a type of nagging in the interpretation and emotional response of the afflicted. Children with speech difficulties may withdraw because of revolt at being unable to make themselves understood. The cripple may withdraw because of revolt at being unable to exert his ego in play competition with normal children. child who has undetected faulty vision or color blindness, or the child who unknowingly does not hear well may withdraw because his sincere attempts in his best possible accomplishments are looked upon by the teacher or parents as lack of effort. The other most common reactions in such cases are regression, or temper tantrums and fighting.

A child has an ability for interpretation of the attitudes of members of his environment . . . ''

The idea is widely held that the development of a child should be considered as a unitary thing with the realization that in order to have normal and satisfactory adjustment, all of the factors entering must be normal. In this view, a sound mind in a sound body is the ideal, and the development of a sound emotional and social being in the absence of a well body has been denied at least by implication. In the handling of these children very many workers have stressed the importance of establishing compensatory mechanisms for the physical deformity. The ability of the child to develop some special talent as a compensation for its general physical inability has in my opinion, two very definite disadvantages. The first is that very frequently the ability developed is of no social importance, and secondly, very many children do not possess even the latent qualities that are necessary for the development of outstanding perfection in any field. There is also another very definite weakness in a policy of compensation. When the child ultimately realizes, under some special stress, that these compensatory activities are not real, the damage to his self-esteem and to his personality, is likely to be very severe.

In this group we have children who have a physical deformity and handicap. The deformity is not visible, and although the child from a very early age has knowledge of this deformity and the limitations which it imposes, in some instances even greater than the limitations imposed by visible physical deformities, it has been our observation that the presence of these handicaps has not caused any marked deviation from the standards of ordinary conduct or any disturbance in the development of normal social relationships. The data that we have presented in the tables, particularly the factor of social adjustment in the Bell Inventory where no single child in the whole group has fallen below an average social rating, is certain indication of the ability of these children, under proper guidance, to develop perfectly normal social contacts. If this is true, the primary cause of psychic disturbance is not the knowledge of the handicap by the child itself, but rather in the reaction of the child to evidences of recognition of this handicap by the community in which it lives. As a matter of fact, in these particular children the disease does not detract from their attractiveness but rather enhances it. The high color of the person with mitral valvular disease is likely to be considered a very attractive feature, and the large moist eyes of the patient with chronic valvular disease in reality lend a certain type of beauty to the features. To the untrained observer, the child that has attained a physical adjustment so as to be able to carry on most of the ordinary procedures, offers a picture of perfect health. believe that in the type of treatment offered, one very essential factor enters that to a great extent may contribute to the successful adjustment that these children make. It will be noted that with the separation of the child from the family for a period of over one year, the element of overprotectiveness in the home has been definitely minimized. also an interesting observation that the sense of guilt felt by the parent in these cases has to a great extent been dissipated, due to their contact with many children of the same type in other families, and their contacts with parents of other children with heart disease. This sense of parental guilt which is always a serious factor in the management of sick children, particularly children with chronic or incurable illnesses. is often aggravated by the method in which the history of the case is obtained.

When one remembers that the parents start with a sense of guilt and then everyone maybe of a dozen people, physicians, social workers, psychiatrists, etc., in taking the history lays great stress upon the hereditary factors this sense of guilt is greatly increased. They go into great lengths as to whether the father, mother, grandparents, uncles, or aunts, have ever had rheumatism or heart disease, and the sense of responsibility for the condition continues to grow. In our own work, we have made it a special point that in obtaining the familial history of the condition, care be exercised so as not to create the impression that this is a disease visited upon the children even to the third generation.

These children, removed from homes ordinarily on the poverty level, with improper food, with improper facilities, with worried and dis-

tracted parents, are placed in an environment where all of these factors are removed. A feeling of complete security is established by the institutional personnel. Although when the children are first admitted and during the following period of observation the restrictions are very severe, it has been our policy that as soon as it was medically permissible to permit the child up, the assumption was made that the child was perfectly normal and able to do everything that it pleased. It is surprising how easy it is to instill a feeling of complete adequacy at the same time as they are being taught the necessity of certain restrictions and control. Our policy in the institution, briefly, has been to keep the child in bed as much of the day as was necessary, but under no conditions to permit interference with the child's activity in the time that she was permitted up. We found that if this time was carefully apportioned, and the child was constantly watched, there was no danger to the child physically from this procedure.

There is no question in our minds that from the standpoint of the development of healthy mental attitudes, this is the only procedure that will not create a constant feeling of physical inefficiency. A study of the cases offered will show that once these habits of control of physical activity, within the limits set by the child's own condition and recognized by her, have been established, these procedures can then be carried out by the child unsupervised without creating conflicts and dissatisfactions. The acceptance of the idea of the possibility of cardiac death in other children combined with a real ability to ignore its application to oneself has been characteristically present in the interviews. This definite feeling of euphoria that is so characteristic in tuberculosis also seems present in heart disease. When these children were questioned regarding their reactions to the knowledge of the death of other members of this group, the responses although formally satisfactory revealed a total lack of emotional involvement in the death of another child. This was particularly noticeable in view of the fact that the girls had lived together in a relatively small community group over a fairly long period. One or two of the children did say that when very sick, they felt a fear of death but now that their condition had improved, although they realized that other children who had seemed perfectly well had died of heart disease, this did not apply to them. This protective mechanism apparently is of great value in avoiding emotional disturbances on a basis of their cardiac pathology.

In the choice of vocations, as will be seen in Table XII, a very large percentage of the group have expressed the desire of entering into the field of nursing or one of its allied branches. This is to be expected as all of these children have had rather extensive hospital experience, and naturally many of their ideals have been determined by their environment. When these children were informed that nursing opportunities

were closed to them on account of their heart condition, the reaction always indicated that this had been considered if not directly, at least subconsciously, that they were prepared to obtain the same type of satisfaction in some available form when the opportunity to do bedside nursing was denied. The large percentage of the children who plan to do secretarial type of work is not based on the feeling of physical inferiority, but is rather approximately the percentage that would select this type of work in any group from the same social and economic background.

We have presented here a fairly large group of girls with rheumatic heart disease who have been under intensive observation for a relatively long period of time. We find that although many of these children come to us with definite social and emotional maladjustments, under reasonable care, most of these problems may be solved.

The two primary factors that enter into these problems are the parents' guilt complex, and the child's utilization of its organic defect for purposes either of attention-getting or for the development of her own feeling of security. The separation of the child from the home makes it possible to establish healthy normal attitudes both in the child toward their sense of responsibility. This is very much easier with children who have no visible deformity than it could possibly be in children where the deformity is always a cause of comment in the community.

On account of the small number of children involved, none of this material is suitable for statistical analysis, and therefore, is presented only in tabular form.

#### SUMMARY

For the past fifteen years we have had an opportunity to study a large group of girls with rheumatic heart disease. In addition to the physical problems arising from their cardiac disease, the emotional and social development of these children offers an interesting field for study.

A group of 21 girls, who at the present time range between twelve and eighteen years of age, were selected for study. The age of discovery of the heart disease varied from two to ten years, with an average age of seven and one-half years. All of these children had a residential period at the Theresa Grotto Residential School for Cardiac Children at Caldwell, N. J. The average length of this residential period was fourteen months. The average age on admission to the cardiac home was eight and one-half years. The average age of the 21 children in the group studied at the time of the final study was fifteen and one-half years. Complete social service and psychiatric studies were made on all of these children on admission. These preliminary studies to which were added 'complete long-time observation and control, which included physical,

economic, and psychiatric details, furnished the background for the present study. The time interval between the preliminary studies and a final survey varied from two to eleven years.

Two methods of obtaining the data were utilized. The first was a critical study of all the material in the files over the entire period during which the child had been under observation, checked and correlated with a final psychiatric study by the interview method on each child. These studies were felt to be of particular value as these children had been under the personal control and medical supervision of the observer for periods ranging from three to fifteen years. The second method utilized was the testing of the entire group by the "Bell Adjustment Inventory" and the "Thurstone Personality Schedule."

These objective tests gave ratings that corresponded very well with the ratings given by the first method, and may be summarized in the following conclusions:

- 1. Although the child from a very early age has knowledge of the disability and the limitations which it imposes, in some instances even greater than the limitations imposed by visible physical deformities, it has been our observation that the presence of these handicaps has not caused any marked deviation from the standards of ordinary conduct or any disturbance in the development of normal social relationships.
- 2. That one of the important factors in the development of emotional and social difficulties in these children has been the sense of guilt of the parents.
- 3. That another major factor in the development of these difficulties has been the attitude of overprotectiveness in the home based on the fear of the cardiac disease.
- 4. The utilization of a residential school for cardiac children offers an opportunity for the establishment of a successful mental hygiene program and leads to the disappearance in most of these children of undesirable mechanisms established in the home.

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# Critical Review

### THE NATURE OF THE AMERICAN DIET

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L ARLIER reviews in this series have discussed the nature of nutritional needs of the human organism, and the manner in which they may be met. Evidence was presented to establish the prevalence of suboptimal states of nutrition. One must infer from the numerous studies in this field of investigation that a large proportion of the people of this country are handicapping themselves through the inadequacy of their diets. The extent and significance of this status is not appreciated by the population at large nor by many of those concerned with problems of health. This review is directed toward analyzing some data concerning food consumption in this country and comparing the findings with dietary standards designed for optimum nutrition.

In preparing this presentation, publications by various divisions of the federal and state governments have been used freely. The recently published reports of the Committee on Foods of the League of Nations summarize in themselves most of the salient points brought out in this review and have been of great assistance in its preparation.<sup>2</sup> Some of the data and information have been gained from unpublished reports or from personal correspondence with directors of experimental stations and with others who have studied the problem of nutrition in the field. The author gratefully acknowledges the ex-

cellent cooperation and assistance of these agents.

Several methods of approach have been used in studying the nature of food consumption. By correlating the number of people with the data regarding production, import, and export of various commodities. apparent per capita consumption may be computed. Surveys of foods purchased or consumed in sample areas may be taken as representative of the area as a whole. Individual variation in food habits as compared with the community as a whole may offer an index of the degree of uniformity of nutritional practices. Data so obtained may be studied in terms of geographic locality, occupation, economic and social level, age of the constituents of the population, race, size of family, or other constants. Each of these methods is subject to error in compilation of data and of interpretation. However, discrepancies lose significance when the same qualitative conclusions are reached through studies conducted in different sections of the country, by independent investigative personnel, using diverse methods of attack. The massed statistics do not offer strictly quantitative information, yet they indicate the prevalence of grossly deficient diets, and even greater prevalence of suboptimal states.

A high degree of correlation may be demonstrated between the adequacy of diet and many constants in the manner of life of the

individual or the community. The lower the expenditure for food, the greater the likelihood of deficiency; yet in every level of outlay for food, much improvement could be accomplished through more intelligent choice of foods. Suitable diets are favored through home production of the necessary components; however but few areas use their facilities efficiently to insure adequate seasonal or year-around supplies of certain foods. Studies of production show that the supply of some essential foodstuffs must be increased considerably if the average need for such commodities is to be met. In the upper economic brackets, the per capita consumption of necessary foodstuffs falls significantly below a desirable level. Probably the first step necessary for the betterment of the nutritional state is to make the people aware of the advantages of optimal nutrition in contradistinction to maintenance or subsistence levels.

#### STANDARDS FOR NORMAL NUTRITION

Factors needed for nutrition include the following: biologically valuable protein; the minerals which enter into the composition of the tissues or which are used in metabolism; the various vitamins; sources of energy. The latter may be supplied as carbohydrate, protein, or fat. Qualitatively, nutritional needs are similar at all ages; quantitatively, they vary both as to the total and as to the amount of individual constituents. During the period of growth the requirement for proteins and structural minerals is relatively or absolutely greater than in the adult. In the latter, moreover, the requirements for replacement are greater than is generally recognized. During the period of early maturity, needs may continue at levels approximating those of active growth if optimum nutrition has not obtained during the earlier years. The quantitative need for some factors will vary not only with age, but also with the nature of the occupation, geographic location, and other constants. Some data have been expressed in terms of the adult male unit, on the premise that requirements for the remainder of the population are aliquot proportions of this unit. Such data may be misconstrued as applied to the child, especially as regards protein and bone-building minerals, since the requirement of the child is not a linear function of that of the adult. This is particularly important in evaluating the consumption of milk, eggs, and meat.

Foodstuffs vary greatly in their content of nutritional essentials. They may be characterized roughly into two groups, those which offer appreciable concentrations of minerals, vitamins, and first-grade proteins and those which are principally valuable as sources of energy. The first group includes foods such as milk and its products, eggs, fruits, vegetables, fish liver oils, fresh meat products. The second includes some articles which have certain nutritional virtues other than their calorie content, but which for various reasons are less valuable than other forms of foods. Examples include the starches, sugars, and most fats; the highly milled cereals are included with the starches in this category. The foods in the first group are often designated as protective foods because of their dependability in completing the quality of the diet. Whereas inadequacy of calories is encountered in the lower economic levels of some regions, this is far less common than deficiency in protective foods. From the monetary

standpoint, the nonprotective starches, sweets, and fats are the cheapest sources of energy, whereas meat products are among the most expensive. Cereals in their native form have nutritive properties sufficient to rank them as protective foods; as consumed, however, most of their valuable constituents have been removed or destroyed in the processing necessary to insure keeping qualities or to enhance their appearance. The protein of legumes and of some cereals, while noteworthy in amount, is less available for tissue building than that from meat or milk. When supplemented with liberal amounts of milk, the quality of cereal protein is assured. Unmilled cereals constitute a valuable source of iron, a dietary essential which is lacking in some areas. However, Sherman has pointed out that the increased use of cereals usually results in a lessened intake of calcium and of vitamins A, C and G.<sup>3</sup>

Sherman states that the American dietary as a whole tends to supply an excess of protein, but insufficient calcium, and that, whereas proof is less positive, there is reason to believe that a large proportion of American families are underinsured as to vitamins A, C, and G.<sup>4</sup> His observations concerning protein apply to the adult rather than to the child; on theoretical as well as practical grounds, there is reason to believe that the diet of the child is frequently deficient in protein. The League of Nations Committee emphasizes the need for supplementary vitamin D because of the very limited amounts of this vitamin in foods commonly eaten and because exposure to sunlight is often inadequate.

In assessing the quality of diets, various levels of nutrition must be recognized. A publication of the Department of Agriculture offers diets designed to meet different degrees of availability of foodstuffs. The first of these will supply all essentials in liberal amounts and assure the optimum state of nutrition. The second is adequate, but offers less margin of safety against deficiency. The third is of minimum adequacy; it barely meets nutritional needs and does not provide for much storage nor for unusual needs. The fourth is designed for use in nutritional emergencies; not with the idea that it meets nutritional needs, but with the hope that its use will lessen the inadequacy which would result from unguided use of food at times when allowances lie below the minimal level. Even though such diets are not recommended for continuous use because of their inadequacy, they are superior in quality to those commonly used in some marginal groups of our population.

In outlining desirable nutritional practices, the optimal diet should be the objective; it should be one which will supply everything which will contribute toward the achievement of radiant health and normal development. Several authorities have published such diet lists for the various ages of childhood and for the adult. These are in general agreement that the child should receive the following each day: one quart of milk; one egg; two or more liberal servings of vegetables, one of which should be of the pigmented variety, and preferably one should be caten raw; similar amounts of fruit, part of which should be fresh, preferably raw; liberal amounts of butter; fresh lean meat or fish once a day, if possible; cereal products, sweets, and fats in amounts sufficient to complete the diet, but not to replace any of the

foods specified in the foregoing. This agrees essentially with the recommendations of Mrs. Rose. those of the Committee on Nutrition of the League of Nations, and those of the Department of Agriculture of the United States. The diet advocated by the Department of Pediatrics of the University of Iowa for the control of tooth decay is similar to these others, but it includes in addition a teaspoonful of cod liver oil daily, throughout the year.7 In the minimal and emergency diet recommendations of the Department of Agriculture, the level of milk intake is maintained at 11% and 1 pint a day, respectively. To meet the economic need, larger allowances of legumes, dried fruits and cereals are suggested, with some reduction in the amounts of lean meat, fresh fruits and vegetables, and eggs. In each of the diets cited in the foregoing, preponderant use of protective foods will be noted; they supply from 40 to 771/2 per cent of the total calories. In contrast to these values the diets employed in 224 American families, as analyzed by Sherman, offered only 20 to 30 per cent of the calories as protective foods.8

In evaluating the diet practices of a community it is much easier to detect and define trends than to determine with accuracy the exact intake of an individual or of a community. Marked differences exist from family to family; food use varies with the season of the year and with the financial status. Conclusions may be directed toward certain aspects of the diet or toward the status of nutrition as a whole. One may consider individual variations, or the general condition within the community. To simplify these problems in this review, attention has been directed toward the degree of consumption of milk, eggs, meat, vegetables and fruits as an index of the use of protective foods, and of sugar and cereal products, representative of the less valuable foods.

#### CONSUMPTION OF MILK

It is necessary to distinguish between data pertaining to the use of total milk products and those concerned with the consumption of milk and cream. In the manufacture of butter, which accounts for about a third of milk production, the protein and mineral content remain in the buttermilk. Whereas some of this will be ingested as cheese, the average consumption of the latter is not great enough (4 to 5½ pounds per year per capita) to represent much of the milk diverted for buttermaking. The use of gross figures has led in some instances to the apparent use of milk in amounts considerably greater than actually consumed. Wherever possible, the data quoted in the discussion to follow include only milk or cream used as such or as ingredients in other foods.

The gross daily milk production in this country in 1934 averaged 98,940 million pounds. If prorated among the population of the United States, this would allow somewhat more than 0.8 pint per capita. Of the total, 12,008 million pounds were consumed as milk or cream on the farm where it was produced. In addition, about 60 per cent of this amount was retailed by the producer in adjacent areas. The remainder was used for buttermaking on farms, fed to calves, skimmed or separated for butterfat, or sold at wholesale. Prorating that consumed on the farms, the allowance per capita of the inhabitants of rural areas is 0.57 pint. When the consumption and

production are considered regionally, the average obtained varies from a low of 0.36 pint per capita in the North Atlantic states to a high of 1.06 pints in the west North Central region. These amounts may be augmented slightly through the retailing of milk in the rural areas, but in general the evaluation probably is fairly correct. Moreover, it is in fair accord with the reports from various state authorities as to observed average consumption.

Data for urban consumption of milk are available through the results of numerous local surveys. In Baltimore the average daily per capita consumption in the higher income district was 0.874 pint, as compared with 0.697 pint in the lower income area. In Philadelphia from an official survey including 3,413 families, the average was 0.65 pint. A house-to-house survey in Burlington, Vt., showed that the younger children received more milk than those who were older, the average daily intake ranging from 1.19 pints to 0.41 pint. In Richmond, Va., the average consumption was calculated to be 0.414 pint daily, as compared with 0.741 pint in New York City. In New Hampshire, eight cities between 12,500 and 77,000 population reported average consumption varying from 0.71 to 1.12 pints. In several large cities on the Pacific coast, the average milk consumption was from 5 to 6 pints per week per capita (0.7 to 0.85 pint). In southern industrial districts, the range was from 3 to 8 pints per week per capita (0.4 to 1.1 pints).

When individual variation from the local averages is studied, a better picture of the status is obtained. Thus, in a study of all the children of preschool age (over 6,000 children) at Gary, Ind., it was reported that 57 per cent had no milk on the day of the survey, and that only 19 per cent had received a pint or more. In the highest income group 38.5 per cent had received no milk. 17 In a Kentucky survey it was reported that milk consumption averaged almost a pint a day, yet 28 per cent of the children received less than that amount. 18 In a Virginia survey it is stated that 40 per cent of a group of children of preschool age did not receive milk, and that of the school age group only 32 per cent received as much as a pint a day. 19 In Texas only 28 per cent of a group of 993 children received as much as three cups of milk a day.20 In Alabama not more than 50 to 60 per cent of the farm families studied produced enough milk for their own use; among the negro farmers the condition was still less favorable.21 In village studies in Maine it was estimated that children of preschool age averaged 2.7 cups, school children from 1.7 to 2.4 cups per day.22 In two small towns in Massachusetts, one located in a dairy area and the other not, 64 per cent of the children in the former received a quart of milk daily, whereas only 16 per cent in the latter city used that amount.23 In 895 farm homes in New Hampshire, 73 per cent of the households owned cows and averaged 0.9 quart consumption per capita per day. The remainder of the families, however, used but little milk.24 South Carolina 10 per cent of the rural population are said to have no cows and to purchase almost no milk. Of the 47 per cent who had but one cow, no provision was made for the family's milk supply while the cow was dry.25

From the foregoing, it is evident that in most regions, a varying proportion of the children may receive a desirable amount of milk.

At the same time, there is as large or a much larger number whose milk allowance is decidedly below the amount necessary for suitable nutrition.

To appreciate the need for stress on the level of milk consumption for the child, it is necessary to review his needs for protein, calcium, and phosphorus, and to consider the potential food sources of these three essentials. According to accepted standards, the child needs a gram of protein per pound of his proper body weight each day, or about 70 grams for a child of ten years. A quart of milk will supply half of this amount. An average serving of lean meat will furnish from 12 to 18 grams of protein; an egg, 6 grams; a large dish of oatmeal, about 4 grams; three slices of bread, about 3 grams. The total protein equivalence of these foods will barely meet the predicted need. If the milk allowance is reduced to a pint, it will require an additional liberal serving of lean meat to replace its protein value. If no milk is used, protein deficiency seems inevitable. In view of the ease of ingestion and the low cost of protein in the form of milk, its advantages seem obvious. But milk offers other advantages as well. The calcium need of the child is estimated at a gram a day; this amount is needed to permit the calcification of the hard tissues to keep pace with their growth in volume. A quart of milk a day will supply this amount in a readily usable form, together with a desirable amount of phosphorus. The calcium content of lean meat is negligible.26 Whereas some other foods may be used as a source of part of the calcium, their concentration of lime salts is such that a disproportionately large amount must be ingested in order to acquire the necessary supply. Balance studies have shown that with suitable amounts of vitamin D, the child may maintain a desirably positive calcium balance with 24 ounces of milk a day; the larger amount lessens the hazard of inadequate mineralization of bone.<sup>27</sup>

#### CONSUMPTION OF EGGS

In comparison with the recommended level of consumption, the observed use of eggs parallels in its inadequacy that of milk, with outstanding variations above and below the general average in different regions and during different seasons of the year. The summary of average per capita consumption of eggs from the League's report is set at 199 per annum, or 0.55 egg per day. In some of the midwest states the average level of consumption is considerably greater than this number; the average value reported from certain districts of Kansas was 9 eggs per week;<sup>28</sup> Montana, 10 eggs per week;<sup>29</sup> in Nebraska, during a period of low market value for eggs, the average consumption approximated two a day per capita.<sup>30</sup> In Wisconsin, on the other hand, a report of egg consumption during the winter months indicated that with high market value, very few were used.<sup>31</sup> In a Kentucky survey the consumption averaged an egg per family per day; eggs were almost entirely absent from the winter diet, whereas at the time of greatest yield, only 62 per cent of the children received eggs as often as twice a week. It was stated that eggs were considered as money and that in their stead less marketable products were used.<sup>15</sup> Other reported averages of weekly per capita use were 5.5 in Florida;<sup>32</sup> 4.5 in Georgia;<sup>33</sup> 6.3 in Illinois as a whole, but 8 when the rural consumption alone was considered;<sup>34</sup> 4.6 in Louisiana;<sup>35</sup> 5.5 in Missis-

sippi;<sup>36</sup> 5 in New Hampshire;<sup>24</sup> 8 in rural Ohio;<sup>37</sup> 4 in South Carolina;<sup>38</sup> 3 to 4 in the South Appalachian region;<sup>18</sup> 6 in Utah.<sup>39</sup> It will be recognized that these studies must be corrected for regional and seasonal peculiarities and that much individual variation in consumption exists. In the Gary study, which was cited in the survey of milk consumption, it was found that 60 per cent of the children had eaten no eggs on the day preceding the questioning.<sup>17</sup> In the southern districts eggs were used in fewer numbers by the negro population than by the remainder.

#### CONSUMPTION OF MEAT

The average annual consumption of beef, pork, and mutton in the United States during the years 1930-34, according to data presented by the League of Nations Committee, totalled 136.5 pounds per capita.2d The largest part of this, 78.1 pounds, was pork, which because of its high fat content cannot be considered as equivalent in its protein value to the other meats. While much of the fat may be removed and used as lard, large amounts of it are consumed in the form of bacon and salt fat meat. The protein content of pork side meat is only half that of equivalent weights of beef. Correcting the above values for the relative protein content, one may estimate that the average per capita protein ingestion as meat amounts to 27.4 grams per capita per day. This is supplemented by the consumption of poultry and of fish, which is not large considering the country as a whole, but which is quite large in some areas. When used, however, it usually replaces, rather than supplements, the use of other protein foods. In rural Illinois, the annual per capita consumption of chickens is quoted as 10;34 in rural Kansas, 15.28 In the states adjacent to the Great Lakes much fish is used; the amount is not stated.40 In a Florida survey consumption of fish averaged 9 pounds a year per capita for whites, 12 pounds for negroes.

Marked regional differences are noted in habits of meat consumption. Consumption of beef is greater in urban than in rural areas; in the latter the use of pork predominates, especially in the South. In a regional Kentucky survey it is stated that 60 per cent of the rural families have no meat other than fat salt pork for eight months of the year; this however is served three times a day to children and adults alike. Aside from its fat and its low content of protein, this form of meat is of questionable nutritional value. A similar condition prevails throughout the greater part of the South. In general, consumption of meat in these states is too low; yet a disproportionate amount of the food budget as a whole is said to be diverted to this expensive form of food.

Although in parts of the country the protein consumption of the adult members of the population probably exceeds their need, it is doubtful whether many cildhren of any region receive much more than enough to meet their requirements. In the southern states it is very questionable whether a considerable proportion of the population at any age receive protein in sufficient amounts. This is dependent on the low consumption by these individuals of milk, eggs, and lean meat. The high level of consumption of cereals and of legumes probably lessens this deficiency in considerable degree, but in view of the fact that protein from vegetable sources is less valuable to the

human organism than that from milk or meat products, the safety of such a regimen is still open to question. Moreover, dependence on cereal sources for protein usually results in a reduced intake of calcium, vitamins, and iron. From dietary studies alone, one would predict the prevalence of nutritional anemia and hypoproteinemia among many of the inhabitants of the southern states.

#### CONSUMPTION OF FRUITS AND VEGETABLES

Data expressing the total consumption of fruits and vegetables in rural areas are inadequate, due to lack of accurate information concerning the amount of these foods produced and consumed at home. Yet by observing the number of families raising gardens, the nature and amount of material typically produced, the type and amounts of foods canned, stored or otherwise preserved for winter use, and the extent to which such families purchase these types of foods, an estimate can be made concerning the adequacy of their ingestion. Field surveys indicate quite unanimously the high percentage of farmers who make little or no use of the garden for the production of fresh foods during the growing season, and canning and storage are not utilized in an effective manner. In a Kentucky study18 it was reported that whereas most families had gardens, only few varieties of foods were raised. Green beans were the vegetable most commonly raised, and the planting of carrots and green vegetables was small in amount. Very few foods were stored for winter. Canning, chiefly of tomatoes, was inadequate in amount. Only half of the families studied stored even potatoes for winter use; in their stead, dried beans were used daily. Although the region was adapted to the production of fruit, 80 per cent of the families raised none, whereas others had only a few peaches or apples. Wild blackberries were used extensively and comprised the only fruit canned by two-thirds of the families. The situation in New Hampshire was quite similar. Although most families had gardens, few used them effectively. Vegetables and fruits were used in season, but home canning averaged only 20 quarts per family. Seventy per cent of the families have trees which bear fruit, yet only half of the people serve fruit twice daily.24 In the southern states where all-year gardening is possible, the winter garden usually consists only of a patch of turnip greens or of collards. Practically without exception, reports from rural areas throughout the country indicate that although the consumption of fresh foods may approach adequacy during the growing season, their use is very limited at other times, that provision for storage and canning is not adequate, and that but few fresh products are used during the seasons when they must be purchased. Where it is possible to estimate the average annual consumption in terms of their proportion to the total diet, they represent possibly half the amount that has been recommended. In some areas the diet is devoid of vegetables other than dried beans and consists throughout the winter of beans, bread, fat salt pork, and syrup,

#### CONSUMPTION OF CEREAL PRODUCTS AND OF SUGAR

Cereal foods usually are palatable, cheap, and satisfying as far as the appetite is concerned. It is natural that they should fill a large place in the diet. If restricted to a proper proportion of the total, their use is to be encouraged. However, when together with fats they usurp a major place in the diet, their use contributes to malnutrition. Moreover, they usually are used in a form which preserves little of their vitamin and mineral content. At best, they contribute nothing unique in nutritional value; as often used, they supply only a form of cheap energy. The use of cereals in a condition approximating their native state would greatly increase their nutritional contribution; this is not practicable because in such form they often are less palatable, are less adaptable in the preparation of baked goods, and become rancid or infested very readily. Limited amounts can be eaten as cooked cereals; many of these as marketed offer little other than starch and vegetable protein. If eaten with milk or cream, the latter has the more outstanding nutritive worth.

Sugar has little to commend it as a food, other than its cheapness, ready availability, ready combination with other foods, energy value, and pleasant flavor. Yet this food comprises the source of a fifth to a sixth of the calories in the average American diet. The data quoted by the League's Committee<sup>2d</sup> indicate an average daily per capita consumption of 4.5 ounces, equivalent to 540 calories. In a New York rural survey, the consumption by younger children was estimated at 3 ounces a day; for men, 5 ounces.<sup>41</sup> The average daily per capita consumption of wheat in 1932-35 is quoted at 0.61 pound, or over 1,000 calories.<sup>2d</sup> In Table I the percentage distribution of calories is expressed in terms of the diet recommended for the child of ten to twelve years by Mrs. Rose,<sup>6</sup> that observed in 224 typical American families as quoted by Sherman,<sup>8</sup> and the results of a federal survey of diets of families of wage-earners and clerical workers in North Atlantic states.<sup>42</sup>

TABLE I

	PERCENTAGE DISTRIBUTION OF CALORIES			
NATURE OF FOOD	PRESCRIBED	OBSE	RVED	
Cereal products	20-25	38.2	30.25	
Fats	13-14	10.32	17.14	
Sugar and sweets	6-8	10.06	12.37	
Eggs, meat, cheese, etc.	7-8	20.76	14.60	
Milk and its products	34-38	8.08	9.79	
Vegetables and fruits	17-18	12.04	14.74	

The values expressed in the two general diet averages represent foods served to both children and adults, whereas the prescribed foods are designed specifically to meet the needs of the child. The latter will be somewhat higher in milk products than is essential for the adults, although the same regimen may be used for each with profit. The preponderant use of meat products in the observed dietaries compensates in an inadequate manner for the deficiency of milk, in a form which is economically extravagant. The preponderant use of cereals and sweets and lessened consumption of vegetables in the observed dietaries is noteworthy. Data regarding sugar consumption indicate that more is consumed than meal surveys reveal. Possibly this is due to the consumption of candy and other sweetened products apart from the meals. Otherwise it suggests an inordinate use of sugar by some individuals as compared with the average data for the whole group.

### ECONOMIC FACTORS IN THE NATURE OF THE DIET

Within the lower brackets of income, there is direct relationship between the expenditure for food and the quality of the diet. In a comparison of purchases by families whose weekly food expenditure ranged from \$1.20 to \$4.17, the use of each type of foodstuff increased with the amount expended for the diet as a whole; the most marked increase was in vegetables and fruits, and next in meat products. Of these, fresh foods showed gains out of proportion to dried products, vet the use of canned fruits increased markedly. Other aspects of the same study, which was conducted in typical areas of the North Atlantic, Pacific and east South Central industrial districts revealed that individual diets may fail to correspond in adequacy to the level of expenditure.16 It was found that in each region some families managed to maintain quite satisfactory dietaries even with minimal outlay, whereas similar numbers failed to receive satisfactory foods even at the upper level of expenditures. With the negro families it has been noted that with increased outlay, the tendency is to buy larger amounts of the same poorer quality foods used by those in the lower brackets. In each industrial region studied, the average food consumption was very inadequate with minimal expenditure, and did not become dependably satisfactory except in the higher brackets. A weekly expenditure of \$2.00 or more per capita appeared necessary as a minimal average allowance for adequacy.

In the rural studies reviewed, it may be observed almost without exception that food consumption is determined in large measure by the nature and amount of produce raised at home. In most areas local production for home use falls far behind its possibilities, and measures for the preservation of food are generally inadequate. Where products have a good market value, they are more often sold than used. In the single-crop regions, especially those farmed by small renters, there is resistance to the use of lands for garden purposes. During the time when such crops had low market value, the use of the land for small gardens increased, but with restoration of good prices the practice was discontinued.

Another obstacle to the improvement of the level of diets is the ignorance and indifference which is commonly encountered in regard to the body's food needs. The people have become so accustomed to eating as a source of pleasure or as a means of silencing hunger that they do not recognize nutritional requirement beyond these ends. Campaigns of education through demonstration units, school programs and extension work in farmers' organizations probably will prove the most effective agencies. While elevation of the standard of living in the underprivileged groups will relieve some of the more glaring nutritional defects, the habits of whole communities will have to be altered before good conditions will prevail in them.

In a considerable proportion of the children of these who are financially able to afford good food, the intake falls below the requirements for optimum health. This must be attributed to unfamiliarity with the importance of proper cating. In the terms of elements of nutrition, these deficiencies concern chiefly the intake of calcium, protein. vitamin D, and in lesser measure vitamins A, C, and G. In terms of

foods, these deficiencies reflect inadequate use of milk, fruits and vegetables, and deficiency of vitamin D either as sunshine or as one of its food sources such as cod liver oil.

In a recent discussion of dietary inadequacies in the British Isles, a correspondent quotes Mellanby on the delay in general utilization of the nutritional discoveries of the past two decades.43 If the problem had been one which applied primarily to adults rather than to the oncoming generation, it would have received more acclaim. To expect healthy, strong adults, it is necessary to feed them well during the period of growth, not merely to prevent disease, but to build for the best possible health. The comment continues by stating that the superior athletic ability of the Finns as compared with the British youth is less mysterious when it is remembered that the daily milk consumption of the former is three times as great as that of the latter.

#### STIMMARY

Statistics concerning average food consumption and surveys of eating habits establish that the American diet is decidedly below the standard of optimum adequacy. Even among those who can afford the best, many individuals receive poor diets. In the poorer groups. the incidence of poor nutritional habits is vast. Such a situation inevitably lowers the level of health of the population. Certain measures would aid in the correction of these conditions. Educational measures should be directed toward familiarity with relative food values. This should lead to the increased use of milk and its products. vegetables, and fruits. In rural areas the encouragement of home production of valuable foods and their preservation for use throughout the year would be most important. In urban areas it is necessary to familiarize members of households with proper distribution of expenditure for food so that less may be spent for foods of low biologic worth, and more for those which are more essential. In many areas, the readjustment of food habits would be relatively minor, whereas in others it will be necessary to bring about marked reorganization of the dietary regimen if outstanding malnutrition is to be corrected.

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# American Academy of Pediatrics

# **Proceedings**

# SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

JUNE 2-4, 1937 Waldorf Astoria Hotel, New York

#### Round Table Discussion on Diabetes

Chairman: Elliot P. Joslin, M.D., Boston, Mass. Assistant: Priscilla White, M.D., Boston, Mass

CHAIRMAN ELLIOT P JOSLIN—Before proceeding with the round table discussion, I would like to say a few words about the incidence of diabetes in children I believe that there are about twelve thousand diabetic children under the age of twenty years and eight thousand under the age of fifteen years in this country now, whereas before insulin, the frequency was one thousand cases per year. Dr. White feels there is one diabetic child for every eight thousand normal children. The exact incidence is not definite. Reliable statistics indicate that there are probably be tween ten thousand and eleven thousand diabetic children living in the United States. The number of unclassified cases is going way up

The mortality before insulin was discovered was quite high. One thousand children afflicted with diabetes died per year in the United States in the preinsulin days. The discovery and use of insulin has changed this gruesome picture greatly. Now one child in one hundred dies per year. The present day diabetic child will outlive the doctor.

Years ago it was difficult to settle the question whether or not a child was a diabetic. The repeated venipuncture resorted to years ago was an obstacle to diagnosis Today a capillary blood sugar test for diagnosis is a relatively simple procedure and has replaced the venous blood sugar determination

An interesting question is how many patients with glycosuria later turn into true dirbetics. This question has received special study by Dr Marble at Colorado Springs, will be reported upon, and will appear in the near future in the Journal of Medical Sciences. Patients with renal glycosuria should be watched during life

A blood sugar determination in children having upper respiratory infections is unreliable. It should therefore be remembered that a blood sugar determination for drignosis does not count in the presence of an infection, i.e., "cold in the head"

A word should be said about the duration of life of juvenile diabetics. Here again the picture has changed. No diabetic patient under nineteen years of age died in Boston in 1935. In Stettin there was no death in coma during one recent year. I quote from a recent study by the Metropolitan Life Insurance Company. A child afflicted with diabetes at the age of ten years and treated has a life expectancy of 317 years. Now compare the life expectancy of a diabetic individual at the age of sixty five years with that of a normal person at the same age. The life expectancy of a diabetic at the age of sixty five years is eight years, that of an apparently so

called normal good health non-diabetic person at the same age is twelve years. In other words, the average diabetic child today has a better chance of living longer than the average doctor, for it has been repeatedly demonstrated that the average practitioner enjoys his art of medicine for a period of approximately thirty years.

Now, what are the causes of death from diabetes in children? (1) Diabetic coma, (2) pulmonary tuberculosis, (3) infections, (4) hypoglycemia, (5) accidents, (6) miscellaneous causes.

Table I gives the incidence of death from these causes since introduction of insulin in 1922.

TABLE I

RESULTS OF FIFTEEN YEARS' TREATMENT OF 1,063 DIABETIC CHILDREN—AUGUST, 1922-1937

	LIVIN	G 959							1	<b>JEAD</b>	104		
			DEATHS-NONCOMA						_				
DATE	CO	MA	TUBE LO	RCU- SIS	INF TIO		GLYC		ACCID	ENTS	MIS		-
1922-1927 Total 35 Av. duration	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	•
2.7 yr. 1927-1932	32	91	0	0	3	9	0	0	0	0	0	0	
Total 27 Av. duration 4.7 yr. 1932-1937	11	70	2	8	3	11	2	8	1	4	0	0	
Total 42 Av. duration 9 yr.	18	43	7	15	11	25	2	5	1	2	3	7	

Diabetic coma is the most important single contributing cause of death in the

Page 256, line 5 below table:

"Even with the use of insulin today a greater percentage
of children are dying with diabetic coma than was the case
for all diabetics (adults and children) before the time when
insulin was discovered."

"A more

What happens to children who do not die of diabetic coma? By referring to the chart you will find that in our study during the first five-year insulin period the average duration of life was 2.7 years and that there were no deaths from tuberculosis, during the second five-year insulin period the average duration of life was 4.7 years with only two deaths, or 8 per cent, and during the last five-year period with insulin seven deaths were due to tuberculosis, or 15 per cent. Thus in toto of nine children who had diabetes and died of tuberculosis, the shortest duration of life was five years and the longest fifteen years.

DR. ALFRED FISCHER (New YORK CITY).—Do you do a routine tuberculin test in addition to x-ray of the lungs?

DR. WHITE .- We hope to test each child in camp this summer.

DR. CARL FISCHER (PHILADELPHIA).—Is there a greater tendency for the child to develop adult tuberculosis if he has had a primary tuberculosis?

CHAIRMAN JOSLIN.—I think so because all our patients have had calcified areas showing earlier infection.

DR. J. C. MONTGOMERY (DETROIT).—What is the incidence of positive tuberculm reactions in diabetic children? DR. WHITE.—Forty per cent of diabetic children in Boston have positive tuberculin tests and 65 per cent tracheobronchial adenitis with calcification.

DR. MONTGOMERY.—Is there any explanation for the terribly high incidence of tuberculosis seen in diabetic children?

CHAIRMAN JOSLIN.—No, except this one point. Many of the children have been "contacts" with adults who had open lesions.

Page 257, line 11: reulous patients develop tuber-

pulmonary tuberculosis. ... however, statistics indicate that this incidence has risen within the past few years from one in one hundred cases to one in thirty.

DR. SCHONFELD.—What is the outlook of a diabetic patient who acquires tuberculosis?

CHAIRMAN JOSLIN .- Diabetics do very well in sanatoriums.

DR. SCHONFELD.—Does the management of tuberculous patients afflicted with diabetes differ materially from that of nondiabetic tuberculous individuals?

CHAIRMAN JOSLIN.—No, the management is essentially the same as with non-diabetic tuberculous patients.

DR. JOHN M. HIGGINS (SAYRE, PA.).—Is the incidence of tuberculosis in diabetic children on the increase?

CHAIRMAN JOSLIN.—The death rate has been going up; the incidence of new cases has been going down.

DR. HIGGINS.—Is there reason to believe that, with appropriate management of the case, the incidence of tuberculosis death rate in diabetic children will be still less?

DR. WHITE \_\_Yes.\_\_Also page 257, line 30:

"A curious observation is that after three years following come one diabetic out of every eight develops tuberculosis."

ears follow-

during the second, and 25 per cent during the third five-year period.

DR. ALFRED FISCHER.—In regard to infections in diabetic children, such as acute appendicitis, which, by my experience, is way over the average, is there any theoretical explanation? Does diabetic tissue show less resistance to infections?

CHAIRMAN JOSLIN.—We have had many cases. Appendicitis is often fulminating. (He cited example of patient dying from diabetic coma after being operated for appendicitis.) Pain, nausea, and vomiting are frequent symptoms of diabetic coma. The appendicitis problem works both ways. Now a reaction from protamine insulin complicates the clinical picture because of nausea and vomiting. Rule is: operate if in doubt.

Four children in all died from hypoglycemia, one child died in one of our best hospitals before the result of the micro-blood sugar determination came in. Another child received two hundred units of insulin; Dr. White loaded this patient down with carbohydrates, but she did not survive. Will Dr. White tell about the suspected hypoglycemia death yesterday?

DR. WHITE.—The girl referred to had had diabetes for seventeen years. An appendectomy was performed, and on the fourteenth day she was ready for dis-

charge. She had given herself fifteen units of insulin at 11:40 A.M. She appeared so ill following the injection of insulin that the nurse thought that she had hypoglycemia. Thereupon one pint of orange juice was administered to the patient. The patient died after complaining of pain in the chest. The clinical diagnosis was pulmonary embolism, which was confirmed at autopsy. At autopsy there was a fatty liver. The pancreas weighed less than 60 grams.

CHAIRMAN JOSLIN.—Here is an instance which would have been incorrectly labelled and diagnosed death due to insulin shock if an autopsy had not been performed. Many cases of supposed death from insulin shock have proved to be due to pulmonary embolism. Therefore, when you have patients who are said to have died of insulin shock, think twice. According to Dr. Hartmann, hypoglycemia occurs also in nondiabetic children.

In our series of patients there were only two deaths due to accidents. Among the miscellaneous causes, two deaths were due to pregnancy (one eclampsia and the other following an abortion). One death was due to cerebral hemorrhage. Interesting in this connection are the observations of Bourchadart, who in 1875 said that he had not seen a single pregnancy among diabetic women. In 1905 Naunyn stated that he had seen one pregnant woman who had diabetes. Dr. White has studied the records of three hundred pregnancies among two hundred diabetic women. Now it is quite a luxury to have a diabetic pregnancy. It costs a lot to have a diabetic pregnancy, as Dr. White will tell you.

DR HIGGINS.—Will you sketch the care of the newborn infant whose mother is a diabetic?

DR. WHITE,—A premature infant born of a diabetic mother does not breathe well. Upon birth the infant is placed in an oxygen helium chamber, which consists of a mixture of 25 per cent oxygen and 75 per cent helium. Such a procedure, at present, must necessarily be limited for hospital routine.

The chief danger to these infants is from asphyxia. In addition to the oxygen chamber, referred to, we aspirate them. Many of these babies have fluid in bronchi. An attempt is made to stimulate the respiratory center and improve circulation. Alpha-lobelin and coramine are frequently employed.

Water by mouth is not given during the first twenty-four hours. Mouth feeding is also avoided during the first twenty-four hours. After that period, routine feeding is followed. Babies of diabetic mothers are usually hypoglycemic.

A blood sugar estimation is made at birth and every three hours. If the blood sugar remains above 50 mg. per 100 c.c., we do not worry about hypoglycemia. A blood sugar above 50 mg. is normal. On the other hand, if the blood sugar drops below 50 mg., glucose is administered parenterally, not by mouth. Fifty cubic centimeters of a 5 per cent glucose given intramuscularly, bilaterally, is of value.

DR. HIGGINS .- Is your rule invariable? Do you permit breast feeding?

DR. WHITE.—The procedure outlined is that form ordinarily followed. We are primarily concerned about the welfare of the mother. Lactation is often defective in diabetics. Then, too, many of the infants have been delivered by cesarean section.

CHAIRMAN JOSLIN.—We have a pediatrician and expert premature nurses present at the births of children of diabetic mothers.

DR. HIGGINS .- After the first twenty-four hours, do you proceed along the orthodox method?

DR. WHITE.-Yes.

DR. HIGGINS.—Approximately, how many of the offspring of diabetic mothers fall below 50 mg. in blood glucosef

DR. WHITE .- About 20 per cent.

DR. HIGGINS.—What is the prognosis for such infants?

DR. WHITE.—If they survive the first twenty-four hours, they usually progress favorably. However, such infants should be constantly watched.

DR. HENRY F. HELMHOLZ (ROCHESTER, MINN.).—Why do you not give glucose routinely?

DR. WHITE.—The procedure is undoubtedly wise, but we are studying the blood sugar curve of these infants.

DR. HELMHOLZ.—What strength parenteral sugar do you administer by clysis?

DR. WHITE.-Five per cent glucose.

DR. HELMHOLZ,-Any irritation?

DR. WHITE.—No. In his paper the day before yesterday, Dr. Hartmann advocated three minims of adrenalin (1:1000) to forestall hypoglycemia.

DR. MONTGOMERY.—Can you tell us approximately how many of your babies have required glucose parenterally?

DR. WHITE.-About 20 per cent.

DR. FRED W. BUSH (ROCHESTER, N. Y.).—What is the percentage of hypoglycemia in newborn? We have one newborn with blood sugar of 49 mg. per cent.

DR. WHITE.—The data for newborn children are insufficient in number. We had one baby with 9 mg. per cent blood sugar.

CHAIRMAN JOSLIN.—Hypoglycemia may occur in the newborn of diabetic mothers. It is by no means universal. Be careful not to kill with treatment. Be careful about giving fluids by mouth (asphyxia?). Glucose might best be administered rectally or subcutaneously. Dr. West in Dr. Bertnard Smith's Clinic in Los Angeles is studying this subject.

DR. EARL F. KELLY (PAWTUCKET, R. I.).—What is your educational program? Do you educate the mother, child, or both?

CHAIRMAN JOSLIN.—Both. A two-year-old child comes in with diabetes. The responsibility often falls on the child at ten years, especially if the mother does not have control of the child.

DR. ALLEN.-What do you do with the adolescent rebelling against regime?

CHAIRMAN JOSLIN.—This is a common behavior reaction, especially among girls. (1) Association with others. Most striking example was a fourteen or fifteen-year-old girl, mentally disturbed, with colitis and abdominal pain. Treatment: large private school away from home where there were three other diabetic girls. (2) Obese child found herself by helping her father in business. (3) Summer camps.

(4) Boarding school. (5) Explain that the disease is not necessarily progressive.

(6) Example of successful careers of others.

DR. ALVAH L. NEWCOMB (CHICAGO).—Do you need pyschiatric help often? CHAIRMAN JOSLIN.—Yes.

DR. ALLEN.-What do you do with the poor boy who is rebelling?

CHAIRMAN JOSLIN.—One learned radio. Another has behaved nicely at Prendergast Preventorium, which is a sort of boarding school.

DR. WALTER LEVY (New York City).—What is the frequency of lipemia in general with diabetes? (He cited a case with blood cholesterol and blood fat of 900 mg. which responded readily to regular insulin.) What are the subsequent connections to arteriosclerosis?

CHAIRMAN JOSLIN—These questions cover a tremendous field. Our last patient with lipemin with diffuse vanthomatosis died in New York City without an autopsy. Lipemin retinalis has been observed in 1 in 1000 diabetics. Hypercholes terolemia is rure today in any pitient taking carbohydrate, 150, and a moderate quantity of protein and fat

DR HIGGINS—I would like to ask a question that is not exactly a pediatric problem. Do you make an effort to discourage diabetics from marrying?

DR WHITE —I do not think we have ever done so, although diabetes is a hereditiry disease. We might, however, discourage child bearing

CHAIRMAN JOSLIN.—It is not so bid when one diabetic marries another who is nonaribetic, but we are absolute in saying that two diabetics must not marry and have children

DR HELMHOLZ —Have you known of any such cases, in which two diabetics married, and the result of such pregnancies?

DR WHITE-Yes Twenty four per cent of the offspring developed diabetes

CHAIRMAN JOSLIN -Dr. White can give you some interesting figures relative to this incidence.

DR WHITE -The following figures are self explanatory

	COPPECTED EXPECTATION	IDENTIFIFD
Cro-s between two diabeties	100%	24%
Cross between diabetics and carriers	40%	10%
Cross between carriers	16%	4%

DR J B. STONE (RICHMOND, VV) —Is there any difference in the incidence of complications among the newborn diabetics and newborn infants of nondiabetic mothers?

DR WHITE—Of the newborn of diabetic mothers 60 per cent developed asphyin Congenital defects have been reported in the literature. Also there is the problem of hypoglycemia, as has already been referred to

DR E ALBAGER (CINCINAUTI, OHIO).—How many days must chapse before you can consider the newborn infant out of danger?

DR WHITE - Ifter the first twenty four hours

DR M HINES ROBERTS (ATLINTI, GI) —What is the association of asthra and diabete-  $\hat{i}$ 

DRS JOSLIN AND WHITE -About one per cent Have you had any cases?

DR ROBERTS-Two recently.

DR WHITE—Dr Kerrs by the association is very infrequent. The whole problem was discussed at the American Association of Physicians, about three years ago

DR H CHANDLER CLARKE (New ROCHELLE, N Y)—What is the relation ship of allergy to diabetes? I have under my care a child who every time he cries, gets a neurodermititis. His blood fasting sugar is 98 mg per 100 cc

DR WHITE—It is an established fact that allergy runs in families of dialetics, tending to skip the patient

DR CLARKL - Are such patients good risks for tonsille tomy?

DR WHITE-We have never had any trouble with them

#### Protamine Insulin

DR WHITE -The mortality rates of the preinsulin era long ago answered in the affirmative the question, "Should insulin be used in the treatment of juvenile diabetes?" But wonderful though insulin was, the fundamental characteristics of juvenile diabetes, severity, instability, and progression, led to a certain amount of dissatisfaction. The severity and progression are indicated by the tendency toward elevation of the fasting blood sugar in successive years of duration until the fifth year, when stabilization has generally occurred. To counteract this, students of diabetes in the past have administered large doses of insulin late at night or in the early morning. Though effective, too often they were omitted by parents and children who feared night hypoglycemia. The child, whose fasting blood sugar is three or four times the normal, awakens with exhaustion and nausea, and is unable for many hours to carry on the normal activities of a child. This was the state of affairs until 1933 when Dr. Hagedorn formulated his new working hypothesis, discovered protamine insulin, and for clinical trial administered it to patients with severe Juvenile diabetes who, treated with the old technique, had a characteristic W shaped blood sugar curve. When he administered a dose of regular insulin in the morning and protamine insulin at night, he flattened the curve to that of a normal or mildly diabetic individual

The work with protamine insulin advanced rapidly, for Dr. Best demonstrated the physiology of the single time technique already advocated by Wilder and Campbell, namely, that the size of the dose of protamine up to a certain point controlled the duration of action in the body. In the Connaught Laboratories zinc was added to protamine, doubling the efficiency of the pieparation.

The technique of desugarizing a new patient with protamine insulin is not difficult, and the size of the does is based upon the age of the patient.

YEARS	DOSE (UNITS)
 0- 5	10
5 10	20 20-30
 10-15	20-30

This may be increased gradually to forty or fifty units, but, if this limit is leached, accessory doses of regular insulin are indicated.

With long standing cases the replacement is more difficult. Though it is not a hard and fast rule, we generally begin with two units of protamine to one of regular insulin. When the fasting blood sugar drops, the need for regular insulin decreases

From September, 1935, to June, 1937, some four hundred children have been ad Justed to protamine insulin, 97 per cent with the single time technique, only 10 per cent with protamine insulin alone. The age, the duration, and consequently the severity of diabetes have controlled the size of the dose of insulin

The need for regular insulin is indicated by the level of the blood sugar at 11:30 AM. The two doses of insulin are administered separately but at the same time.

The carbohydrate content of the diet is not quite so liberal with protamine insulin as with regular insulin. Most of the time we employ 2 (C): 0.9 (P.): 1(F.) ratios. The total calorics have been based upon basal metabolic studies; the rates of growth, upon periods of prolonged observation at camps and boarding schools, and the appetite of the child.

AGF YFU'S	CALORIES	
1 5 6 10 11-15 16 20	1000 1400 1600 1800 1800 2000 1800 2500	

The great advantage of protamine insulin is, we believe, not only the greater comfort of the single time technique, but the number of hours of controlled diabetes, which should have a profound effect upon the prevention of degenerative complications in the future.

DR. L. HAYS (Tulsa, Okla.).—If population is considered in general for diabetic as well as nondiabetic individuals, have you any idea how in many cases such urines would be sugar positive?

DR. WHITE.—I have no idea. I do not think such work has ever been carried out.

DR. CLARKE.—Frequently I receive word from the laboratory when a request for a tolerance test is posted, asking me if I want a two-hour tolerance test. Will you explain what is meant by a two-hour tolerance test and which form of tolerance test you prefer?

CHAIRMAN JOSLIN.—For the glucose tolerance test, 1 gram of glucose is given to the patient per pound of body weight. A blood sugar estimation is made in one hour and again in two hours. If the blood sugar is 200 mg. per cent with sugar Page 262, line 17:

"If the blood sugar is 130 milligrams per cent fasting (venous or capillary) or below this figure, he is not diabetic."

use both the

sugar level of 200 mg. per 100 e.c. or above, or a venous blood test of 170 mg. per 100 e.c. or above is quite diagnostic. Never diagnose a person as a diabetic on a single tolerance test. Wait a little while, and do another.

DR. CLARKE.-How often are readings taken?

DR. WHITE .- One-half hour, one hour, and at two-hour intervals.

CHAIRMAN JOSLIN.—Never make a diagnosis of diabetes unless sugar is present in the urine.

DR. ROBERT A. KNOX (WASHINGTON, PA.).—What are the important complications seen in diabetic children?

DR. WHITE,—There are seven important complications met with in diabetic children:

- 1. Coma.
- 2. Loss of resistance to infections, local and general.
- 3. Premature development and degenerative changes.
- 4. Deficiency disease.
- 5. Metabolic disturbances of the skin.
- 6. Dwarfism.
- 7. Hepatomegaly.

Of these complications we shall discuss two, dwarfism and hepatomegaly.

Failure of growth and development has occurred in 5 per cent of our diabetics. We define as dwarfism or pseudodwarfism those cases in which the height deviates from 4 to 13 inches below the standard for age. The condition has followed rather than preceded diabetes. Besides the failure of growth these children have delayed dentition, silky hair, lanugo hair, delicate skin. The intelligence is generally normal. The condition appears to be a physiologic contradiction, for it is overactivity rather than underactivity of the pituitary that we associate with diabetes. Whether dwarfism is the result of diabetes or its treatment or whether they are coincident conditions remains a problem for future solution.

Male predominance was the rule.

The children have been treated with high caloric, high protein diets, later with the addition of thyroid, and still later the addition of growth hormone; we believe we

have obtained good results with hormone therapy. The rates of growth doubled after its administration. However, these children were also treated with protamine insulin, and we believe the acceleration of growth is greater with protamine than with regular insulin. The physiology for this has been demonstrated by Dr. Wilder, who has shown the greater retention of nitrogen with protamine than with regular insulin.

Enlargement of the liver has been observed in 5 per cent of our diabetic children. The size of the liver is not insignificant. The edge can be traced in the lower abdomen and x-ray reveals it often in the pelvis. Many of the children are dwarfish. They have large, protuberant abdomens with dilated veins. The kidney, the spleen, and the heart may also be enlarged.

Many have had severe attacks of abdominal pain.

The nature of the enlargement is not clear. It may be due to glycogen or fat or both. None has come to biopsy or autopsy. Chemical tests reveal little. A rise of blood sugar occurs after the administration of adrenalin and the blood fat studies are essentially normal. Liver function tests have revealed no abnormality. The lipolitic ferments were diminished.

The lesions have been produced experimentally by Best, by the omission of cholinc in the diet and the administration of anterior pituitary substance. We have treated such cases with betaine hydrochloride, a cholinelike substance, and also by protamine insulin; the better results were obtained by protamine insulin. This was reported by Hanssen of Hagedorn's clinic.

DR. KNOX.—Upon what criterion do you base your standard of undergrowth?

DR. WHITE.—Upon standard height scales. If a child's height is more than 4 inches below the standard—this is considered abnormal.

DR. KNOX.—What is the percentage of retarded growth in diabetic children?

DR. WHITE.—Five per cent of diabetic children fail to grow normally.

CHAIRMAN JOSLIN .- Has anyone tried antuitrin-G?

DR ALFRED FISCHER.—No results. Also bad reactions to thyroid medication.

CHAIRMAN JOSLIN.-When epiphyses have closed, cases are pathetic.

DR. WHITE.—One child grew at nineteen and twenty years.

DR. JOHN A. MONTFORT (BROOKLYN, N. Y.).—I have used it with excellent results. One child gained 1% inches in eight months.

DR. KNOX .-- What is the dosage, and how do you gauge the anterior pituitary hormone?

DR. WHITE.—Three cubic centimeters are administered every other day only to patients whose cpiphyses are open.

DR. LEROY STOKES (HAVERHILL, MASS.).—What is the incidence of enlarged livers in diabetic children?

DR. WHITE.—Five per cent of the patients have enlarged livers.

DR. CLARKE.—Do you also find enlarged livers in younger diabetic children? Does the enlargement of the liver bear any relationship to the deposition of subcutaneous fat, skeletal growth—dwarfism?

DR. WHITE.—Yes, it seems that everything in the growth and developmental system is retarded, the bones, development of the teeth, etc.

DR. CLARKE.—Does the use of protamine insulin improve such conditions?

DR. WHITE.—Yes.

DR. NEWCOMB—The children treated with protamine insulin appear more like normal children. They are leaner, with smaller abdomens. Gain in height is accelerated, particularly in pseudodwarfs with large livers.

DR HAYS—Is it true that the adjustment of a long stinding case of juvenile diabetes is more difficult by means of protamine insulin?

DR WHITE -Yes

DR C V. CALVIN (BRIDGFPOLT, CONN) -Will you discuss the reactions in cident to the administration of protamine insulin?

DR. WHITE.—At first it was thought that protaining insulin did not produce severe reactions. We now know that it does. Protaining insulin may produce severe reactions—usually delayed. Nausea, vointing, and headache are seen in patients who receive protaining insulin. The skin sometimes becomes dry instead of moist. In this respect protaining insulin differs from the reaction of regular insulin. As a matter of fact, the patient will resemble one in coma, and differ entiation must be based upon laboratory methods. This reaction is seen from 4 to 6.1, M

DR. GEORGE W CALDWELL (New York CITY).—Have the diets and caloric requirements changed since institution of protamine insulin?

CHAIRMAN JOSLIN .-- Not essentially.

DR J. B STONE (RICHMOND, VA).—Do diets have to be changed with the use of protamine insulin?

DR. WHITE—Before the days of protamine insulin we used two to one, or three to one carbohydrate fat ratio. With protumine insulin we employ a two to one carbohydrate fat ratio

DR STONE -What would you say is the great advantage in the use of protamine insulin?

DR WHITE—The one time technique of administration of insulin (before breakfast), the assurance of normal growth and development, and the prevention of complications

CHAIRMAN JOSLIN.—I would like to sax that from a st ?

Page 264, line 35:

"In this survey there was not a single child patient up to the spring of 1937 treated by protamine insulin who ever went back to regular insulin." (Since that date there have been few such cases.)

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of injections
figure out the
end fat?

DR WIIIE — We have not answer that schedule (vicin). He works better with the older patient who actually eats with moderation. How many give less carbohydrate with protamine insuling (Majority used about the same earbohydrate)

DR CLARKE -Why do some couldren do bridly when the treatment is changed from insulin to protamine insulin?

CHAIRMAN JOSLIN—With protamine insulin you do not begin to get the blood sugar under control for several drys. The change of the blood sugar curve is a slow, not a rapid energy. This takes time and patience. Protamine insulin means that you must spread the meals out during the day. Protamine insulin acts "while you sleep". It acts between meals and controls the patient for twenty-four hours. Results are from summation of effect. The use of protamine insulin

does not necessitate living on protein so much. Patients can therefore utilize their carbohydrates better, for, as you know, diabetics do not have much stored carbohydrates. One of the big advantages is simplicity of treatment. Do not change dosage frequently. Be slow in conclusions.

DR. ALPER M. WISE (Brooklan, N. Y.).—What do you do with patients who absorb protamine insulin irregularly?

CHAIRMAN JOSLIN .- I just do not know.

DR. MONTGOMERY.—Is protamine insulin preferably given at night instead of the morning?

DR. WHITE.-With adults it has been used but not with the child in our clinic.

DR. NEWCOMB.—What has been your experience with U 80 protamine?

CHAIRMAN JOSLIN.—We have been unable to detect any difference in action and have so informed the manufacturers. We expect reactions from mistakes with the greater concentrations. I know of no fatal cases with protamine insulin, 5 or 6 fatalities with the regular insulin. Of cases of all ages treated with protamine, five hundred were treated with protamine insulin alone, seven hundred fifty treated with protamine and regular insulin.

DR. HAROLD L. VOGEL (JACKSON HEIGHTS, N. Y.).—Can you give both regular and protamine insulin in the same syringe barrel?

CHAIRMAN JOSLIN.—Dr. Butler mixes the two insulins and gets, to some extent, the effect of each. Our results were not very satisfactory. We hope to have eventually a clear instead of a cloudy protamine.

DR. WHITE.—We attempted to layer the two insulins. This is difficult. Some of the regular will be converted to slowly acting insulin. But, if we mix the two insulins and give relatively more of the regular and less of the protamine than previously given, we may get the desired effect.

DR. ROCKWELL M. KEMPTON (SIGNAW, MICH.).—How is one to judge whether to prescribe protamine insulin alone or protamine with a supplementary dose of regular insulin?

CHAIRMAN JOSLIN—Usually one is able to get a normal morning blood sugar with protamine insulin alone, but loss of control will appear at noon or in the afternoon. Regular insulin is prescribed in the morning to manage the forenoon hyperglycemia and glycosuma. Dr. Himsworth of England had written reporting good results the next day, when protamine was prescribed at 11 P.M. A patient with a carbohydrate of 240 required 40 units of protamine at the onset. Insulin requirement has now dropped to 12 units, but this is a most exceptional case. Protamine protects the child's health.

DR. WISE .- How low a blood sugar have you seen without a reaction?

CHAIRMAN JOSLIN.—Do you mean the lowest blood sugar encountered in diabetic patients without the appearance of symptoms?

DR. WISE.-Yes.

DRS. JOSLIN AND WHITE.—Thirty milligrams per hundred cubic centimeters without symptoms.

DR. WHITE -Twenty milligrams per hundred cubic centimeters without bad symptoms.

DR. MONTGOMERY.-Will you tell us how you manage the acute diabetic at the onset of an acute infection?

DR. WHITE—We do one of two things: reduce the diet to C. 150, P. 50, F. 50, and either administer regular insulin every three hours according to the fraction, or continue with protamine insulin and give supplementary doses of regular insulin at noon, 6:00 P.M. and 10:00 P.M.

Regular Insulin Units	ΙĴ	10	5
Color of Benedict Test	Red or	Yellow	Yellow Green
	Orange		

DR C. H. WAYMULLER (BLOOKLYN, N. Y.).—Do you nearly always have to give intravenous glucose for protamine insulin shock?

DR. WHITE -No, not as a rule.

DR. WISE .- How much carbohydrate ein a diabetic utilize?

CHAIRMAN JOSLIN.—None of us knows. It is a very difficult thing to standardize a diabetic's tolerance.

DR. CLARKE -I would like to ask two questions for practical purposes:

- 1. A diabetic youngster is on regular insulin. I desire to change over to pro tamine insulin. Is it a rule to give two thirds of the regular dose of insulin?
  - 2. In a growing child, do you give a nigh protein diet?

CHAIRMAN JOSLIN —1. All of us who work with diabetics have individual ideas, sixty units of insulin a day, divided into three doses of 20 20 20. I would give 20 units of regular insulin in the morning and then would hedge and give 30 or 36 units of protamine insulin.

Question 2 was answered by Dr. White .- The ratios we use are C2, P.O.9, F.1.

CHAIRMAN JOSLIN.—I have not seen a single instance of insulin atrophy (subcutaneous fat) with protamine insulin. I have seen such change when ordinary insulin was used.

DR W. J. SCOTT (Detroit, Mich ) .- I would like to present the case history of two juvenile diabetics and ask your advice about their treatment.

H. B. K, Jr. was born Dec 9, 1932, and was first seen by us at the age of three months and was followed regularly until the age of two years. He had no acute infections except one mild cold during this period. At the age of two years, he weighed 26 pounds 10 ounces, and was 32 inches tall. We felt that his slight under nutrition was due to excessive activity. He was not seen again until Sept. 25, 1935, a period of nine months, because he had been, to all intents and purposes, well. The mother brought him in to see us because his appetite was unusually good, and he was failing to gain in weight. He also was drinking lots of water. The physical examination at this time was entirely negative except for the above mentioned under nutrition. Urmary sugar 4 plus. Fasting blood sugar (Sept. 28, 1935) 105 mg. Two days later, the blood sugar was 320 mg. An appropriate diabetic diet was outlined with 5 units of regular insulin twice a day. The weight at this time was  $271_2$  pounds, a gain of only 14 ounces in nine months.

This child has progressed very satisfactorily, his parents having adhered rigidly to the prescribed diet. He has hid a few minor respiratory infections without any serious complications and without any marked disturbance in his metabolism. His weight at the present time (May 20, 1937) is 39 pounds and his height is 39¼ inches. At present, he is receiving 6½ units of regular insulin in the morning and 7 units in the evening. Blood sugar determination (May 20, 1937) was 80 mg. Previous blood sugars hid varied from 66 mg. to 105 mg. Occasionally, he has mild hypoglycemic reactions in the middle of the day following strenuous exercise, but these are readily controlled by orange juice and sugar.

In view of this boy's very satisfactory progress, would you advise changing him over to protamine zinc insulin and how and when would you do it?

D. S. G., male, born Jan. 2, 1936, and when first seen by us at the age of a few weeks, was entirely normal and remained so until November, 1936, when the mother began to notice that the child had excessive thirst with consequent polyuria. weight on Nov. 14, 1936, was 21 pounds 5 cunces and, except for an acute cold, the physical examination was negative. However, a specimen of urine showed sugar 4-plus and acctone 3-plus, and the sugar was identified as glucose. Blood sugar. two days later, was 100 mg. Obviously we could not make a diagnosis of diabetes at this time but told the parents he should be treated as a potential diabetic. We did not have to wait long, because two days later he began to vomit and the following day became very drowsy and acidotic. Blood sugar on this date (Nov. 19, 1936) was 348 mg. He was accordingly hospitalized and his glucose tolerance determined. He was placed on an appropriate diabetic diet with 8 units of protamine zinc insulin before breakfast. We have followed him at intervals since this period and his weight has risen from 20 pounds 2 ounces (Nov. 19, 1936) to 29 pounds 5 ounces (May 28, 1937). His present height is 33 inches. During the month of February, 1937. he had an acute respiratory infection with suppurative otitis media, from which he made an uneventful recovery without any visible trace of acidosis. We have had gradually to increase the dose of insulin, however, from 8 units to 14. At the present time he is doing quite satisfactorily on a dosage of 12 units. Blood sugar determination (May 28, 1937) was 100 mg.

In view of the satisfactory progress of this boy so far, and in view of the very early onset of the disease, what would you say, in the light of your experience, as to the possibility of such a child's eventually being able to regain normal pancreatic function with discontinuance of insulin therapy?

CHAIRMAN JOSLIN.—I would recommend protamine insulin for these children. As reported in world literature about fifty children have developed diabetes under one year. Five children have developed diabetes under one year in our series—youngest seven months.

ALVAH L. NEWCOMB, Chicago. HENRY H. PERLMAN, Philadelphia. Secretaries.

# SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

## Round Table Discussion on Glomerulonephritis

Chairman: John D. Lyttle, M.D.
Assistants: Allan M. Butler, M.D.
Lee Farr, M.D.

CHAIRMAN LYTTLE.—In their studies of postscarlatinal nephritis, Escherich and Schick thought that the kidney had early in the course been sensitized in some way so that in the second or third week small amounts of pathogenic substance circulating would cause an injury while at any other time that amount would be tolerated without any reactions. This pathogenic material and the reaction called acute glomerulonephritis are believed to be connected in some way with antigenantibody reactions known to be going on at this time. Shick noted the analogy between course of events in scarlet fever and the group of allergic reactions just being studied at that time. Since then a lot of kidney damage has been done to various animals, but the experimental studies have not been of great help to the clinician. Masugi in 1928 began his studies on nephrotoxins. This work seems important and I have asked Dr. Farr to discuss this type of experimental nephritis.

### Experimental Nephritis

Dr. FARR.—The ctiology of acute hemorrhagic nephritis is a most obscure subject. Clinical investigations have done little to shed any bright light on the cause of the disease, and experimental efforts have fared but little better. At Dr. Lyttle's request, today I shall not disease the streptococcus etiology, the hypothesis of exposure to cold or the factor of heavy metal poisoning, but shall confine my remarks during the limited period to a discussion of a type of experimental nephritis with which we have recently been working and which may or may not be of value in explaining the phenomena seen in human nephritis.

The study of nephrotoxins (which term I shall use throughout as designating an antikidney serum) goes back to Lindemann in 1900. He injected guinea pigs with rabbit kidney and found that if he injected this resulting guinea pig sera into rabbits, albuminuria and cylindruria resulted. Pathologic sections of such kidneys showed tubular degeneration. Pearce in 1903 took up and extended Lindemann's observations. Although he was unable to produce an autonephrotoxin, he did show that many of the sera which had been called organ specific depended for their action on the presence of hemagglutinins and hemolysins. Pearce removed these factors by perfusing his organs before injection. Antikidney serum made with such an antigen induced cylindruria and albuminuria, whereas antisera prepared by immunizing with unperfused kidney induced an additional feature-hematuria. antiserum, however, was only relatively organ specific: that is, it exerted its greatest effect upon the kidney but was not without simultaneous effect upon other organ systems. The experimental nephritis which Pearce produced was always of short duration, and the pathologic renal lesion consisted of tubular degeneration with occasional hyaline thrombi in glomerular capillaries. Woltmann and Sata in 1905 and 1906, respectively, repeated Pearce's work and came to the same conclusion regarding the relative specificity of nephrotoxin. Then for a period there was little or no work done with these agents until 1920, when Wilson and Oliver prepared an antikidney serum free of hemagglutinins and hemolysms which produced marked glomerular as well as tubular lesions. These authors considered nephrotoxin to be organ specific since absorption of the antiserum with kidney cells completely removed its nephrotoxic effect. Takeda in 1928 observed fibrin thrombosis and hemorrhage in the glomerular tufts of acutely affected animals as well as tubular degeneration, and he also noted an elevation of blood nitrogen values. Masugi, however, reawakened interest in this field with a series of papers beginning in 1928. He obtained the first convincing evidence of a chronic nephritis induced by the injection of nephrotoxin and made certain functional studies on rabbits in which he had produced this chronic disease. Fahr agreed with Masugi as to the similarity of the renal lesions which were obtained in this fashion to diffuse human glomerulonephritis. In 1935 Klinge and Klepper reopened the subject of autonephrotoxins which they claimed to be able to produce by injecting kidney emulsion and swine serum. Fahr examined sections of the kidneys of these animals and came to the decision that the lesions so induced were different from those obtained by Masugi.

At about this time Dr. Smadel, working with Dr. Swift on a general study of cytotoxic sera, took up studies on nephrotoxin as being very suitable for observation of cytotoxic phenomena. Since this gave us at the same time an opportunity to observe an experimental nephritis, we began a collaborative effort.

The antisera were produced by injecting rabbits intraperitoneally with 10 c.c. of a 10 per cent or 20 per cent suspension of perfused rat kidney. Injections were made on three consecutive days each week for a period of three weeks. Ten days after the last injection, test bleedings were made. This procedure was repeated three times over a period of three months, when the sera were finally taken for use.

It was not possible to determine the nephrotoxic power of the sera by titrating the antibody in vitro. Sera which showed a high precipitin titer might be low in nephrotoxic power, so biological assay was reported too. The good sera were then retained for use.

The nephrotoxic factor in serum is in the globulin fraction. It is not removed by absorption with red cells or serum, is completely removed by absorption with kidney, and is markedly decreased by absorption with liver. The serum is species specific and rat serum had no effect in mice or guinea pigs.

Nephritis was produced in rats by injecting on the average 0.3 to 0.4 c.c. of a good nephrotoxic serum per 100 gm. of animal weight. The same strain of rat was used for this experiment as was used for the serum production. Usually the serum was given in divided doses since in this manner anaphylactoid reactions were avoided while nephrotoxic effect was in no wise lost. The serum was injected intravenously diluted with fresh Ringer's solution.

Before this was done each rat was observed for a control period of about one month when urea clearances, plasma protein and hemoglobin determinations, and urinalyses were done to rule out any preexisting renal lesion. If all these tests fell within the normal range, the animal was used.

Within a few hours after injection of the nephrotoxic sera the animals developed a very severe proteinuria, usually losing protein in the urine in a concentration approximating 40 gm. per liter. During the first few hours when this proteinuria was excessive, the animals for the most part had from moderate to severe oliguria. Urine flow reestablished itself within twenty-four hours as a general rule. The albuminuria, however, persisted in a marked degree for the duration of the disease. Casts were first noted in the urine about the second day of the disease and remained in large numbers until the animal died or made a recovery. About the third day of the induced disease marked subcutaneous edema and ascites were present. At this time the animals presented a nephrotic picture in many respects. There was no hypertension; the blood proteins were markedly reduced; there were massive edema and ascites, the added fluid often amounting to 30 per cent of the animal's weight.

There is marked lipemia and a complete absence of hemorrhagic phenomena. This edematous phase usually clears up in a few days, but may persist as long as three weeks. During this period there is no demonstrable reduction in ability of the kidney to excrete urea as measured by the urea clearance test, and there is no anemia. Their appetites are good, and they are far from feeling as ill as they appear. With disappearance of the edema the plasma proteins show a rise to near normal levels. but the albuminuria and cylindruria are not abated. For the next month there is very little change in the animal, following which period a gradual reduction in renal function, as measured by the urea clearance test, becomes manifest. When the kidnevs are so damaged that the urea-excreting power has been diminished by about 50 per cent, hypertension begins to become an important factor of the disease. After this time the disease marches on to a fatal termination, a progressive fall in the urea clearance, a sustained rise in the blood pressure, increasingly severe anemia, an increasing retention of nitrogen, and a growing plasma protein deficit. When the nephritis so induced is severe enough to cause death within six months, the animal generally ceases to grow within three weeks to a month after injection of the nephrotoxin. Terminally there is a sharp loss of weight, and marked malnutrition becomes increasingly evident, despite the fact that the animals eat their usual rations. We have not been able to demonstrate definite retinopathy in the terminal stages, although it is my impression there is arteriolar constriction but the vessels are exceedingly difficult to visualize because of the severe degree of anemia present. Examination of the bones histologically and calcium and phosphorus determinations

have revealed no abnormalities. Throughout the disease period the animals appear to be able to excrete sodium chloride without difficulty. Occasionally doubly refractile globules are seen in the urine.

Chemically and clinically these rats demonstrate a state which is similar in many respects to human Bright's disease following a streptococcal infection after the nephritis has become chronic.

If relatively large doses of nephrotoxin were injected at frequent intervals, a rapidly fatal nephritis was produced. By using smaller injections and not repeating them, the chronic disease was obtained. A certain number of animals made a complete recovery after exhibiting all of the signs of the disease.

Histologic and gross examination of the kidneys of animals so treated show a variety of pathologic lesions. When the animals are killed during the initial phases of the disease, the kidneys appear rather pale and edematous. Histologic examination revealed diffuse involvement; swelling of the intercapillary substance of the glomerular thickening of the basement membrane and tubular degeneration were prominent. Proliferative changes at this time were inconspicuous, and there was very slight cellular infiltration. The epithelial cells of the tubules were the seat of cloudy swelling and of hyaline droplet degeneration. Many of the tubules were markedly dilated. Collections of cells were frequently present about small vessels in the kidney. These appeared about the fourth day and increased thereafter. These microscopic lesions of the early phase merge into scarring of the glomeruli and tubules. Those examined later in the disease showed well-marked proliferative changes and glomerular crescents. This proliferation of the cells of Bowman's capsule is followed by connective tissue in growth and finally by complete replacement of the glomerulus by scar tissue. In animals with chronic progressive nephritis different individual glomeruli would often show these processes in all stages. The terminal result is a scarred somewhat shrunken kidney with little of its original architecture left intact and practically without functional value. The striking similarity of these kidneys to those which are seen as the end-result of postscarlatinal nephritis is of considerable interest. The fact that this process may under suitable conditions be arrested at any stage or may progress to destruction or recovery is food for thought. The difficulty of demonstrating the presence of these original nephrotoxins is emphasized by the fact that 9 c.c. of serum from a rat with this type of chronic nephritis has been given to a normal rat without effect. The nephrotoxin seems to act as an original noxious agent, which then disappears but which acts in such a fashion as to lay the foundations for a chronic progressive disease with the first blow. The factors operating here thereby causing the lesion to become chronic or to resolve may be in part at least similar to those operating in acute hemorrhagic nephritis.

DR. JOSEPH W. EPSTEIN (CLEVELAND, OHIO).—Your experiments with nephrotoxin indicate an attack on the tubules before the glomeruli are affected. Is this the same in human acute nephritis? Also the fact that there is very little nitrogenous retention with edema—would you say that you produced a nephrosis instead of a nephritis?

DR. FARR.—So far as we can determine, the nephrotoxin affects the glomeruli as well as the tubules. The glomerular changes are not so striking as the tubular changes, but they are definite and always present. The most consistent change is thickening of the basement membrane. In human acute nephritis we believe the glomeruli and tubules are also simultaneously affected, although the tubular changes are not as striking as in the nephrotoxic nephritis.

In regard to the question in which you ask whether we have produced a nephrosis instead of a nephritis since the animal showed an edema with little nitrogen retention, there is no evidence to show that we have actually produced a nephrosis since the animals developing the chronic disease usually died of renal failure; if you

like, you might call it a nephrotic stage, but I believe such artificial discrimination in such experimental disease confuses rather than clarifies.

DR. MYLNOR W. BEACH (CHARLESTON, S. C.).—Does the concentration in the tubule have any effect on the degree of pathology?

DR. FARR.—Your question whether the concentration of supposed excreted nephrotoxin in the tubules has any effect on the degree of pathology cannot be definitely answered. However, I may say that the evidence which we have obtained indicates that the renal injury is dependent solely upon the amount of nephrotoxin injected regardless of its administration, that is, whether it is given in single or divided doses, and from this we may infer that the concentration in the tubules is not the determining factor.

DR. DAVID GABERMAN (HARTFORD, CONN.).—How do you explain Aldrich's idea that the high protein diet results in improvement of his patient's nephritis and general condition?

DR. FARR.—Dr. Aldrich's experiences with high protein diets are consistent with our observations. We have merely determined the quantitative level for optimal assimilation. Patients fed more than this optimal diet do retain and assimilate protein but do not, in our opinion, do it in the most efficient manner. It is my impression of clinical observation also that children on high protein diets do well, but we believe they do better on the optimal protein diet as determined by our balance experiments.

DR. JONATHAN P. HADFIELD (FALL RIVER, MASS.).—What rôle does the creatine ratio play?

DR. FARR.—The creatine ratio or creatine clearance is of value in determining the extent of glomerular involvement. We have used the urea clearance in preference since it is easier to carry out on children, and we believe the results are more informative. However, we have done many creatine clearances and find that creatinine, inulin, and urea clearances all run parallel. We find the urea clearance to be of considerable aid in prognosis since the urea clearance returns to normal frequently months before there is any improvement in the concentrating ability of the kidney and before there is any significant change in the urinary sediment.

CHAIRMAN LYTTLE .- The classical case of acute hemorrhagic nephritis will not fail to be diagnosed. The onset following a streptococcal infection with hematuria, edema, and hypertension is so striking and alarming that the child is usually brought to a doctor. But a large number of cases of acute glomerulonephritis do not show edema or hypertension, and urinary abnormalities which are commonly overlooked may be the only sign of the disease. The nephritis runs a brief course and ends in complete cure without diagnosis or treatment. In discharging a patient with tonsillitis, the practitioner may get a report of urine which shows albuminuria, casts, and cells, and further observation will show that these findings persist for a short time and then disappear. The patient is entirely well, has no extrarenal symptoms, and has good kidney function. It is probably unwise to tell parents that the child with traces of albumin, a few casts, and cells in the urine has Bright's disease. But I think that, even though the disease is mild and transient, the clinician who observes these subclinical changes following a streptococcus infection should bear in mind their prognostic significance and should realize the importance of careful follow-up observations.

Differential Diagnosis.—The following conditions must be considered: (1) Nephrosis, (2) benign albuminuria with minimal microscopic findings (orthostatic albuminuria, etc.), (3) acute exacerbation of chronic nephritis, and (4) embolic nephritis—subacute bacterial endocarditis.

- 1. The differential diagnosis between nephrosis and acute glomerulonephritis should offer no difficulty. Its chief importance is in prognosis. Acute nephritis follows a hemolytic streptococcus infection, and significant hematuria is always present at Edema and hypertension may or may not be present. The edema of nephritis, in contrast to that of nephrosis, is rarely generalized or as massive. Nephrosis may develop following an infection, but the infection is usually a mild upper respiratory involvement, and the hemolytic streptococcus is rarely found. Clinically the important points in favor of nephrosis are generalized edema with apparent well-being and normal blood pressure: from the laboratory, reports are obtained of heavy persistent albuminuria without significant hematuria, no nitrogen retention in the blood, low serum albumin, and high blood cholesterol. Here I should like to point out that at the onset in acute glomerulonephritis we may find moderately low serum protein and high serum cholesterol. This does not necessarily mean a nephritic element in the nephritis. The low serum protein can occur before albuminuria has been present long enough to deplete serum protein. It is possible that these changes in blood chemistry are related to the infection which has set up the nephritis.
- 2. Benian Albuminuria (Including Physiologic, Orthostatic, Malnutrition).—Albuminuria without striking changes on physical examination and without well-marked microscopic findings (cylindruria and hematuria) is commonly seen in young children and during puberty. If the urine is examined repeatedly, the incidence is from 12 per cent to 68 per cent of all children. It is more common in girls. In the majority of the cases serum albumin is the protein identified, but in a number of cases, in addition to albumin, a substance precipitated by acetic acid in the cold is found. A careful examination of the sediment will sometimes show a few hyaline and granular casts and a few red cells. This does not necessarily mean that nephritis is present, for it is entirely possible that the same mechanism which allows protein to leak through the kidney will also allow a few red cells and casts to pass.

Attempts have been made to classify these albuminurias on the basis of some outstanding clinical feature which may accompany the case. It would seem that there are many factors which can be responsible for the condition, but until we know more about the etiology and pathogenesis, we should not be too specific. Physiologic albuminuria is found in the newborn, after exercise, and exposure to cold. It does not persist when the cause is removed. When orthostatic albuminuria is present, the urine voided in the recumbent position contains no albumin or only traces. while the urine voided in the upright position contains variable amounts of albumin and usually a substance precipitated by acetic acid. A few red cells and casts may sometimes be found. This condition is commonly found in boys, from four to sixteen years of age, who are growing rapidly, have signs of vasomotor instability and usually poor posture with lordosis. Kidney function is normal, and serum proteins show no changes. The course is variable, but the condition usually disappears after puberty, and there is no evidence that it leads to nephritis in later life. In a group of children with faulty hygiene-anemia, malnutrition, and foci of infection-Calvin and coworkers found that 60 per cent showed albuminuria. In some children the albuminuria disappeared when the foci of infection were treated or removed. In a second group of children, well cared for and without foci of infection, 15 per cent showed albuminuria.

The chief problem is differential diagnosis. This is an important question and often a difficult one to settle. Even after long study one may not be satisfied that the diagnosis is correct. If one finds repeatedly and without difficulty a number of red blood cells and casts, especially red blood cell casts, the diagnosis is probably mild glomerulonephritis even though there are no extrarenal symptoms and kidney function is normal. We have found the Addis sediment count of great help in differential diagnosis. By this method the number of cells and easts excreted in a period of time is measured and compared with the findings in normal children. If the Addis

count repeatedly shows a definite increase in excretion of erythrocytes, leucocytes, epithelial cells and casts, especially the red blood cell casts, the diagnosis is probably glomerulonephritis. If we can elicit a history of streptococcal infection preceding the urinary changes, this is a point in favor of the diagnosis of nephritis but does not prove it. It should be borne in mind that orthostatic albuminuria may follow postscarlatinal nephritis and also that the erect position may increase the albuminuria in nephritis. The burden of proof is on the physician who diagnoses benign albuminuria. Careful and long-continued observation may eventually clear up the diagnosis. Except for general indications revealed by history and physical examination, no treatment is necessary in benign albuminuria.

There are other conditions not primarily related to the kidney in which albuminuria with microscopic hematuria and cylindruria occurs. In acute infections and in diseases such as intestinal intoxication and high intestinal obstruction and vomiting where dehydration is an important part of the picture, variable degrees of albuminuria, usually with microscopic changes (easts and cells). are observed. This is also true in severe ketosis in children whether the ketosis results from diabetes mellitus, starvation, periodic vomiting, or a ketogenic A well-marked albuminuria with cylindruria is found during the crises In the case of galactosuria reported by of paroxysmal hemoglobinuria. Mason, a heavy albuminuria with cylindruria and microscopic hematuria was observed when the child was on a milk diet, while on a milk-free diet the urine was normal. In acute rheumatic carditis, with or without cardiac failure, jaundice. passive congestion, albuminuria with casts and red blood cells in the sediment are commonly observed. In cerebral conditions such as subdural hematoma, convulsions. and pituitary tumors albuminuria is common.

DR. F. H. ALLEN (HOLYOKE, MASS.).—Are there any statistics to show any increased liability to nephritis in patients with orthostatic albuminuria followed for fifteen or twenty years? Also are such persons accepted as good risks by insurance companies?

CHAIRMAN LYTTLE.—All studies that I am familiar with show no increased liability to nephritis in patients with orthostatic albuminuria. I do not know what attitude insurance companies take.

DR. HADFIELD.—Do you treat all these cases with minimal nephritis findings as potential cases of nephritis?

CHAIRMAN LYTTLE.—The only treatment called for in children with minimal urinary findings is continued observation until the urine is normal.

- 3. In older children the question frequently arises as to whether we are dealing with an acute glomerular nephritis or an acute exacerbation of chronic nephritis. Urinalyses prior to the onset of the symptoms would be of utmost help in the attempt to answer this question. As the differential diagnosis is important in prognosis, the history must be carefully examined in order to answer the question. In chronic glomerulonephritis a story of long-continued ill health with malnutrition, anemia, dyspnea, and fatigue may be elicited. There may be chronic upper respiratory infection, urinary tract signs such as frequency or polyuria, and there may be an episode which, in retrospect, can be translated into the initial attack of acute glomerulonephritis. On physical examination the signs of advanced kidney disease such as well-marked and persistent hypertension with cardiac enlargement, palpable peripheral vessels, and changes in the fundi indicate chronic nephritis. The high blood pressure and enlarged heart, which may occur in acute glomerular nephritis, do not persist after recovery. It is a very difficult problem, and hence the clinician is frequently mistaken in his initial impressions.
- 4. In subacute bacterial endocarditis we may see variable urinary changes which indicate renal damage. There is no way of telling certainly whether we are dealing

with multiple emboli, infarction, or ordinary glomerular nephritis. Good kidney function and the absence of extrarenal signs are not necessarily significant. A benign form of hemorrhagic Bright's disease has been described, which is said to be due to focal nonembolic nephritis. This is an anatomic diagnosis; I know of no way of making this diagnosis clinically.

In the diagnosis of chronic glomerulonephritis the chief difficulty is in differentiating nephrosis from the nephrotic stage of chronic glomerulonephritis. An accurate history and complete laboratory data at the onset of the disease are helpful. Even when most of the findings suggest nephrosis, if the onset has followed an infection with hemolytic streptococcus and was characterized by hematuria and hypertension, the diagnosis of nephrosis is excluded. But glomerulonephritis may resemble nephrosis very closely in its onset and course, and diagnosis will remain in doubt unless retinitis, severe hypertension, or impaired renal function occurs. drich diseards the diagnosis of nephrosis if hypertension is present or if red blood cells are found in the urine. From our own experience and from the literature it seems well established that many children with anatomically proved nephrosis show moderate hypertension and microscopic or even gross hematuria. The significance of this hematuria and hypertension is not known; it does not necessarily mean that the patient has chronic glomerulonephritis. It may, however, signify renal irritation or a mild form of acute glomerulonephritis which can go to complete recovery. The following case is cited as an instance of this:

The patient under close observation showed only nephrotic signs and symptoms in the first five months of the disease. Following streptococcus infection an acute glomerulonephritis (i.e., hematuria, hypertension) developed, lasted three months, and eventuated in complete clinical recovery. The signs of nephrosis persisted. Autopsy seven months after the attack of acute glomerulonephritis showed no lesions in the glomeruli.

When severe hematuria and hypertension develop and persist in a child whose course from the onset has been typical of nephrosis and in whom renal failure eventually supervenes, it is usually assumed that the diagnosis at the onset was incorrect. The majority of children with acute glomerulonephritis recover without developing chronic glomerulonephritis, and the same is true of nephrotic children who develop acute glomerulonephritis. Although it is uncommon for a patient with true nephrosis to develop acute and subsequently chronic glomerulonephritis and renal failure, it sometimes occurs.

In spite of the difficulties which often attend diagnosis, there can be no doubt that nephrosis is a distinct entity; it is clear, however, that signs of nephrosis and of glomerulonephritis frequently occur together in the same patient. When at its onset the disease picture is that of glomerulonephritis, and signs of nephrosis subsequently make their appearance, these signs may be taken to indicate the chronic nature of the original process; the outcome is usually fatal. In such cases the major disease is chronic glomerulonephritis and to them the term nephrosis should not be applied. However, when glomerulonephritis supervenes in the course of nephrosis, it is often an acute process which differs from the disease in uncomplicated form only by a somewhat longer course. It need not necessarily influence the favorable outcome of the nephrosis. In the interest of prognosis, then, the attempt to differentiate between these two processes is eminently justified. Of eight of our cases of nephrosis in which the diagnosis was confirmed at autopsy, hematuria occurred in five and hypertension in six. In addition to the pathologic data, the clinical course in these cases was typical. In nephrosis complete recovery is common after long periods of edema and albuminuria; it is extremely rare in true chronic glomerulonephritis. hypertension, cardiac hypertrophy and renal failure never occur in uncomplicated nephrosis and the almost specific susceptibility to pneumococcus infection is peculiar to nephrosis.

DR. H. G. PONCHER (EVANSTON, ILL.).—If the burden of proof is on the man to prove that a benign albuminuria is not a mild nephritis, is it not reasonable to also say that the burden of proof is on one who finds red blood cells and slight nitrogen retention in a patient with a picture of nephrosis to prove that this is not a mild nephritis? The fact that a patient showing these findings may die of pneumococcic peritonitis and show only minimal glomerular changes and major tubular pathology does not seem to be an adequate criterion for not classifying such a case as a nephritis. May not proved cases of nephritis show exactly such a picture?

CHAIRMAN LYTTLE.—If a patient, onset and course of whose illness have been typical of nephrosis, develops hematuria and hypertension, I suppose one must make a clinical diagnosis of mixed nephritis. Nitrogen retention in nephrosis is not a reliable indication of glomerular involvement. But our experence in the autopsy room, and I think Dr. Butler will agree with me in this, has shown that these patients do not have anatomic nephritis in spite of the presence of hematuria and hypertension. The cause of the hematuria and hypertension in true nephrosis is not known; it may be due to an acute nephritis which can heal quickly. I think we must rely on the anatomic findings as a final criterion of diagnosis, and acute nephritis does not give the anatomic picture we see in nephrosis.

### Treatment of Acute and Chronic Hemorrhagic Nephritis

DR. BUTLER.—The mortality in the acute attack of hemorrhagic nephritis is usually considered to be about 5 per cent. Most pediatricians have felt that another 5 per cent of the cases progress from an acute hemorrhagic nephritis to a chronic progressive type of the disease. Very recently, however, Snoke has reported a follow-up study of 150 cases of hemorrhagic nephritis in children in which he has determined the presence or absence of a renal lesion by the Addis sediment count. From this data he concluded that the nephritis had completely healed in 40 per cent of the cases, had remained active nephritis in 40 per cent, and had proved fatal in 20 per cent. It is quite clear that if these figures are substantiated by further study the generally accepted prognosis in this disease must be altered.

CHAIRMAN LYTTLE.—More recently Dr. Snoke has made a similar follow-up study in Rochester, N. Y. The data on this series do not support the serious prognosis suggested by his San Francisco study.

DR. BUTLER.—Death occurs during acute hemorrhagic nephritis as the result of acute cerebral edema, congestive heart failure, infection, or a rapid progression of the nephritis and a true uremia. The bulk of evidence concerning the etiology and clinical course of the disease indicates that it is closely related to an infection, usually an upper respiratory one, and that a persistence of such an infection tends to prolong or aggravate the nephritis. Obviously, therefore, treatment must include the treatment of any focus of infection which may be related to the attack, in the hope that the severity of the disease will be shortened and recurrence prevented. Usually the related infection has subsided to such an extent by the time the nephritis has appeared that its treatment can be postponed until after the more acute manifestations of the disease have passed. Not infrequently, however, a peritonsillar or retropharyngeal abscess or a mastoiditis may demand immediate operation in spite of the presence of cerebral edema, hypertension, and myocarditis.

CHAIRMAN LYTTLE .- Do you think major surgery should be done in acute nephritis?

DR. BUTLER.—Obviously acute nephritis with cerebral edema, hypertension, and myocarditis does not provide the most opportune moment for major surgery. But operations such as an acute appendix must be done if the ordinary indications for operation are present.

DR. HORACE FRENCH (Lansing, Mich.).—Is there any choice of anesthesias for surgery during the acute or convalescent stage?

DR. BUTLER.—Aside from the indications of a particular operation, anesthesia should be considered as it would be for any patient with a severe myocarditis or cerebral edema.

Bearing in mind that the source of infection must be dealt with at the appropriate time, the immediate treatment is directed toward the cerebral edema, the hypertension, and the myocarditis.

Fortunately the imminence of the appearance of untoward symptoms and their course are readily detected by the degree of the oliguria, the course of the blood pressure, symptoms of increased intracranial pressure such as headache, nausea, and vomiting, the character of the pulse, size of the heart, pulse pressure, and obvious signs of decompensation. Thus untoward signs can be readily detected by the simplest type of clinical observation. It is our conception that the oliguria, hypertension, increased intracranial pressure, and congestive heart failure occur concomitantly and from a common cause-namely, a rather generalized arteriolar spasm which may be the result of a toxin, a nephrotoxin, or some allergic reaction. At least in the absence of any better concept this is a convenient one, for it gives a simple explanation for the effectiveness of the magnesium sulfate therapy which Blackfan and his coworkers have shown to be almost specific. Experimental work recently done by Ruben and Rapoport has shown that the inclusion of magnesium sulfate in the diets of rats inhibits the vascular spasm produced by ergotamine tartrate in rats not so protected. Such a vascular action seems far more likely than an osmotic action, for it is highly doubtful whether such small amounts of magnesium sulfate as are used intramuscularly would result in withdrawing fluid from the edematous brain to the blood stream. Whatever the explanation, magnesium sulfate empirically does lower the blood pressure, relieve the intracranial pressure, and increase the urine volume. Any direct effect that it has upon the heart is less obvious. If the cardiac symptoms are the result of spasm of cardiac vessels, the magnesium sulfate should be as specific for this manifestation of the disease as for the others. On the other hand, the cardiac picture is very similar to that produced by a toxic myocarditis. For this reason intravenous 25 per cent glucose and morphine may be given as therapy for the cardiac failure. There would seem to be some doubt as to whether digitalis should or should not be used. We have not used it extensively enough at the Children's Hospital to draw any conclusions. Dr. Stokes, of Philadelphia, believes it is beneficial. Because magnesium sulfate therapy is so specific, a rather detailed description of the manner of administering it seems justified.

From 4 to 8 c.c. of a 25 per cent solution of MgSO<sub>4</sub>·H<sub>2</sub>O are given intramuscularly to any child whose systolic blood pressure is over 115, or whose blood pressure is observed to be rising, or who presents any significant symptoms of cerebral edema. If the blood pressure has not fallen at the end of two hours or if the blood pressure at a later period begins to rise, the dose is repeated. Concomitantly with parenteral injection, magnesium sulfate is started orally, from 1 to 2 ounces of a 50 per cent solution being given every four hours until the blood pressure has remained normal for twenty-four hours or until catharsis results. Though the magnesium sulfate therapy is accompanied by a loss of weight which runs parallel to the subsidence of symptoms, it is not given primarily as a cathartic but rather as a diuretic. Indeed, experience shows that the oral administration may be repeated every four hours for several days with little or no cathartic effect. Since substituting ten years ago the intramuscular for the intravenous administration of the magnesium

sulfate, we have encountered no case in which intravenous injection was required. All the patients entering the hospital with hypertension and nephritis whose blood pressures have not been lowered by intramuscular magnesium sulfate have been shown to have chronic nephritis or pyelonephritis. Since in such patients magnesium sulfate is ineffective and probably contraindicated, the differential diagnosis between an acute hemorrhagic nephritis and a chronic nephritis should be made before magnesium sulfate therapy is pushed.

In cases in which the oliguria is marked but the blood pressure is only slightly elevated, magnesium sulfate may be started by mouth more or less as a prophylactic measure, but we do not so prescribe it in every case of hemorrhagic nephritis.

DR. MARTIN MALINER (BROOKLYN, N. Y.).—Do you always have a hypertension? What do you call a hypertension? It seems to me you frequently see acute nephritis without a real hypertension.

DR. BUTLER.—Fortunately there is no doubt that such cases occur. In a child under twelve years of age a systolic pressure above 115 and a diastolic pressure above 80 indicates hypertension.

DR. GABERMAN.—Dr. Butler has discussed the treatment of the severe type of acute nephritis usually seen in the hospital, but how about the very early treatment of acute nephritis before the symptoms of headache, hypertension, myocarditis, develop as is seen in private practice?

DR. BUTLER.—General procedures will be mentioned in a moment. Reference to the mild case does bring up the question of the routine use of magnesium sulfate prophylactically. Dr. Lyttle, I believe, has an opinion about this that he might wish to express.

CHAIRMAN LYTTLE.—I believe Aldrich states that magnesium sulfate given routinely in all cases will prevent the development of cerebral edema.

DR. BUTLER.—The prophylactic use of magnesium sulfate may be beneficial, but let us remember, particularly in hospital practice, that an order for 1-2 ounces of 50 per cent magnesium sulfate every four hours has been given and let us see to it that it is stopped at an early date and not continued needlessly.

While using magnesium sulfate medication in the acute or mild case, the patient should not be permitted to become dehydrated enough to inhibit a moderate urine volume. Indeed, one should strive for a rather large urine volume, for as soon as this is obtained, the symptoms subside. To this end fluids should be given in liberal amounts, not restricted. To be specific, a child of six years should have between 1,000 and 1,200 c.c. of fluid per day. Not very much need be said concerning the diet of these children. During the period of acute symptoms the patient will be more or less nauseated and will not want to eat. Sweetened fluid should be given in order to provide an adequate intake of fluid and calories in the form of carbohydrate. Since the edema is due to the oliguria, not to a specific salt retention, restriction of sodium chloride is not important and is cared for by the fact that most sweetened fluids contain little or no salt. As soon as the child feels like eating, he can be permitted to eat. For some days his appetite is such that there is little danger of overeating, and we see no need of restricting his diet except as any ordinary child's diet is restricted.

DR. J. W. BRITTON (ANNISTON, ALA.).—What amount of protein would you use in the diet of a child with acute nephritis?

DR. BUTLER.—The remarks just made pretty well cover that question. At a time when protein might be harmful, the patient will almost certainly not eat it. In

acute nephritis any significant elevation of nonprotein nitrogen or other evidence of severe retention will almost always subside by the time the child feels like eating much protein.

DR. R. M. POLLITZER (GREENVILLE, S. C.).—Please explain the mechanism of the edema in acute nephritis.

DR. BUTLER.—I do not know that I can. The edema of nephrosis and chronic nephritis is usually closely related to the level of the plasma proteins. But the edema in acute nephritis is not accompanied by a low plasma protein osmotic pressure. It is probably related to the effect of the vascular reaction to the toxin or allergic reaction that underlies the disease.

When the hypertension, myocarditis, and gross hematuria have subsided, foci of infection should be dealt with. Tonsils that appear infected on examination, that are associated with enlarged cervical glands, and the history of repeated pharyngeal infections should be removed. I wish I knew how a sinusitis should be treated but I do not. At the Children's Hospital all patients with an initial hemorrhagic nephritis are not subjected to tonsillectomy.

DR. L. M. EARLE (HOLLYWOOD, CALIF.).—Have you any experience in the use of sulfanilamide in the treatment of the underlying infection?

DR. BUTLER .- Not in acute hemorrhagic nephritis. Perhaps Dr. Lyttle has.

CHAIRMAN LYTTLE.—We have used it cautiously in a few cases. If kidney function is impaired, the level of sulfanilamide in the blood must be carefully watched.

DR. B. BENJAMIN (MONTREAL, CANADA).—About what percentage of children with nephritis under your care have not had a tonsillectomy?

DR. BUTLER.—Any answer I gave to that question would be merely a guess, as I have never reviewed cases with that thought in mind. Dr. Lyttle has rather strong convictions on this point and I am sure has quantitative information concerning his patients.

CHAIRMAN LYTTLE .- Tonsillectomy had been performed previous to the onset of nephritis in approximately one-third of our patients. One should never have strong convictions about any aspect of nephritis. However, my attitude on foci of infection in nephritis is somewhat as follows: We do not know which cases of acute nephritis will progress to chronic nephritis, and we are ignorant of the mechanisms of both acute and chronic nephritis. There is clinical evidence that infection in the convalescent period has an adverse effect on the nephritis, and some good observers believe that persistent infection is a factor in the development of chronic nephritis. When chronic nephritis has been established, any attack on foci of infection is useless. Therefore, I recommend tonsillectomy in the ordinary case as soon as improvement sets in and the pharynx is not acutely in-And when the nephritis does not improve on a suitable regime or there is a recurrence of sore throat and adenitis, tonsillectomy is done as soon as the condition of the throat permits. The postoperative flare-up is mild and is not to be compared to the true exacerbation of nephritis that follows a recurrence of infection. I admit the benefits are not proved, but to say that this procedure is harmful is not a valid criticism in the light of my experience.

DR. BUTLER.—The length of the rest in bed should be determined as much by the history of myocarditis and the subsidence of cardiac signs as by the character of the urine sediment. A few red blood cells and a trace of albumin may persist in the urine for weeks or months and may be a relatively poor guide in determining the patient's activities. But a patient should not be allowed up and about while

the heart is still enlarged, the pulse rate elevated, the electrocardiogram abnormal, and erythrocyte sedimentation rate elevated. If these things are normal, I do not see why the patient should not be allowed to be up and about after a few weeks. But great care should be taken for many weeks to avoid exposure to cold or wet and fatigue. In general, the patient should be treated as a cardiac case, neglecting the diet as is done in such cases and judiciously neglecting the urine.

There are a few other points one might mention: first, someone may want to know whether prophylactic medication can prevent nephritis. My answer in the present state of our knowledge concerning etiology is no. Certainly there is no reason for placing the scarlet fever patient on a low protein diet. Likewise the use of antitoxin or convalescent scarlet fever serum probably accomplishes little good. I wonder if Dr. Lyttle agrees.

CHAIRMAN LYTTLE.—I am unable to convince myself that we have any means of preventing acute nephritis.

DR. P. S. RHOADS (EVANSTON, ILL.).—In British fever hospitals it is felt that alkalinization of the urine in the first three weeks of scarlet fever prevents nephritis. Do you think low salt diets are helpful?

DR. BUTLER.—We know of no reason why low salt diets should be helpful in the prevention of acute nephritis. Any such beneficial effect of alkalinization as you mention may be due to the fluid intake and urine volume coincident to alkalinization. It is hard to take alkaline salts without taking considerable fluid.

A second question that may be in your minds is, Can the oliguria be treated by the ordinary diuretics? Our experience indicates that the xanthine derivatives produce little effect. Our opinion is that mercurial diuretics are definitely contraindicated. Third, Is intravenous sucrose effective in relieving the cerebral edema and its symptoms? I cannot answer the question because we have not used it in our clinic as we were a little hesitant in the presence of the oliguria to administer it in large enough doses to be effective. Possibly the drug would not only relieve the cerebral edema but also would have a diuretic effect.

DR. EPSTEIN.—Would you comment on the use of a lumbar puncture in the treatment of the child with acute hemorrhagic nephritis who is in a state of convulsion? Would you do a lumbar puncture or is it contraindicated?

DR. BUTLER.—As demonstrated by Dr. Blackfan these patients may have such an increase in intracranial pressure as to produce a pressure cone. Lumbar puncture if done at all should therefore be done very carefully. Intravenous magnesium sulfate is a much safer and more effective means of treating the cerebral symptoms.

I should like to stress that the magnesium sulfate therapy which is so effective in checking a course of events which may be fatal in hemorrhagic nephritis is ineffective and contraindicated in chronic nephritis. We have no specific therapy for the chronic form of the disease. In chronic nephritis our efforts should be directed toward removing foci of infection and maintaining the patient in as good a nutritional state as possible. Years ago Addis learned that he could usually benefit the nephritic patient referred to him by other doctors because he could abolish the dictary restrictions that had been prescribed. On the other hand, he could usually do little for the patient who came direct to him on a normal dietary regime. Keutmann and McCann have observed no ill effects from high protein diets in patients with moderately severe chronic nephritis. Aldrich and Boyle believed that a group of patients cared for by them did better on a high protein diet than on a diet restricted in protein. They stressed the advisability of including adequate amounts of all the vitamins. As anemia is always present in these patients, a deficiency of iron in the diet should be guarded against. Because chronic nephritis is almost

always progressive and the severity of the condition is changing, it is not unnatural that a diet which is optimal for the patient at one time will not be so at another time. Therefore, the above statements about diet must not be considered to apply to all chronic nephritic children

In the early or latent stage of chronic nephritis there is usually a nephrotic aspect to the disease, and edema may be the most incapacitating symptom. The edema consists of water, sodium, and chloride, and there is ample evidence that such edema may be limited by the ingestion of minimal amounts of sodium chloride. Low salt diets should therefore be prescribed during the nephrotic stage of the disease. In the absence of cardiac involvement such edema is roughly in versely proportional to the concentration of the scrum proteins. It is for the purpose of increasing the scrum protein concentration and making good the loss of protein which occurs in the urine that high protein diets are frequently prescribed at this time. One must not forget that there is a certain amount of evidence obtained from animal experiments indicating that a high protein diet may have a deleterious effect upon the kidney.

DR. PONCHER.—Do you seriously believe that the exceptionally high protein diets are of value in regenerating serum protein? Most children refuse a high protein diet but succeed in regenerating blood proteins anyway.

DR. BUTLER.—Dr. Parr can tell you of some interesting experiments concerning the effectiveness of diets varying in their protein content in maintaining a positive introgen balance and concerning the effect of high protein diets upon the course of nephritis in rats.

DR. FARR—I do not believe that such exceptionally high protein diets are of value in regenerating protein. Our experimental work indicates that protein in the diet is not assimilated by young children when more than 3 gm. of protein per kilogram of ideal body weight is fed. Our evidence shows further that when this limit is exceeded, actually less protein is assimilated than on the 3 gm, per kilogram diet.

DR. BUTLER—As the nephritis progresses, there is an increasing tendency for nitrogen and other retention. Though the urea clearance is increased by a protein diet, ample clinical evidence shows that in the later stages of the disease the protein content of the diet must be limited if significant retentions are to be avoided. Since the inability to excrete the end products of metabolism is the reflection of the kild ney's inability to concentrate such substances in the urine, the name volume should be large enough to provide maximum exception of the substances that should be at low concentrations in the plasma. Papers by Holton and Reliberg and by Newberg and Lashmet and others have clearly proved these points.

Finally in the terminal stage of nephritis when the kidney function is down to 10 per cent of normal, there is an inability to conserve the substances that are of high concentration in the plasma just as there is an inability to excrete those substances that are present in the plasma in low concentration. As a result there is a tendency to excrete a large amount of water, sodium, and chloride. At this stage, therefore, the nephrotic tendency disappears unless cardiac failure complicates the picture. This inability to conserve sodium and chloride may be so marked that an increase in urine volume will not only cause an increase in the excretion of sodium and chloride but will actually result in an increase in the concentration of the sodium and chloride in the urine as the urine volume increases. Because it is essential that such patients have a large urine volume, good treatment coincidently causes the exerction of considerable sodium and chloride per day. We have found that a patient whose plasma sodium was reduced to 126 meg/h, and whose

plasma chloride was reduced to SS meq./l. excreted 3-4 gm. of sodium chloride per day. It is, therefore, important that such patients be given an amount of sodium and chloride in the diet that will maintain for them a balance of these substances and water.

Thus it is clear that no single dictary regime can be followed in the treatment of a patient with chronic nephritis. The course of the disease must be followed accurately enough so that diets may be prescribed that will at all times provide as normal a physiologic state as is compatible with the changing renal function.

DR. BENJAMIN.—Have you observed nephrosis as a distinct entity which proceeded as such throughout the child's life?

DR. BUTLER.—We have had sixteen patients at the Children's Hospital in Boston who we believe had true lipoid nephrosis. Exactly eight of these have for years been well and apparently have completely recovered. Most of the others have been examined at necropsy. Though some had at some period moderate nitrogen retention and a fair proportion of red blood cells to white blood cells and cellular granular casts to hyaline casts and showed involvement of the glomerulae on microscopic study, they had cases of true nephrosis. In each such case the degree of the degenerative changes was such as to result inevitably in glomerular damage. Thus the nephritic part of the clinical and pathologic picture was due to the severity of the nephrosis.

## ANNUAL MEETING OF REGION IV OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting was held on Nov. 4, 5, and 6, 1937, at the Ambassador Hotel, Los Angeles. Sixty-four members, 198 guests, and 46 exhibitors attended, according to the registration. There were 24 exhibition booths. The annual business meeting was held the evening of November 4 and the annual dinner, the following evening in the Cocoanut Grove. At the close of the sessions on November 6, the members attended the Stanford-University of Southern California football game.

Abstracts of the papers presented follow:

### NOVEMBER 4

Recent Investigations With the Tuberculin Ointment Patch Test. Ernst Wolff, M.D., and S. Hurwitz, M.D., San Francisco.

Description of test made by applying a concentrated tuberculin ointment covered with adhesive plaster on arm was given. Control test was made on opposite arm. Positive reaction consists of papule and vesicle formation with redness. A total of 1,075 tests were made on 964 patients, aged three months to fifteen years. Agreement with Mantoux test in clinically active cases.

Advantages are ease of application, absence of pain, and stability of product.

## Pyloric Stenosis. Harman Tremaine, M.D., Boise, Idaho.

General review of subject was given with author's method of treatment outlined. Hydration was accomplished by subcutaneous injection of fluid and intramuscular injection of blood. Usual Rammstedt operation used. Artificial feeding used postoperatively. In the discussion Dr. J. N. Nichols reported 287 cases at Children's Hospital, Los Angeles. Since 1930, 137 cases have been operated with five deaths, four of which were from complicating diseases.

### A Case of Glycogen Storage Disease. Ezra Fish, M.D., Beverly Hills.

A case of von Gierke's disease in child aged two and one-half years, weighing 22 pounds, was reported. Abdomen was enlarged from birth. Liver was enlarged, extending below the umbilicus into pelvis; the edge was smooth and firm; the spleen was not felt. The fasting blood sugar ranged from 40 to 64 mg. per cent. Ossification centers showed development of six months. The blood cholesterol was 175 to 380 mg. The glucose tolerance curve rose slowly to 139 mg. in three hours and returned to normal in five hours. There was an absence of the usual hyperglycemic response to adrenalin. Extracts of whole pituitary gland failed to raise blood sugar, as did prolactin. A peritoneoscopic examination was done during life by Dr. John Ruddock, Los Angeles, who obtained a specimen for biopsy, which confirmed the diagnosis. Dr. Ruddock discussed the technique and advantages of this diagnostic method.

## Calcium and Phosphorus Balance Studies in Children With Latent Hilar Glandular Tuberculosis. William A. Reilly, M.D., San Francisco.

Results: Tuberculous activity is accompanied by a negative calcium balance which could be converted into a positive calcium balance by giving calcium gluconate, 40 to 60 grains per day by mouth, but not by giving cod liver oil. The negative calcium balance diminished during convalescence. There was also a negative phosphorus balance during the active stages of tuberculosis, and cod liver oil diminished this loss.

## A Case of Unusual Fungus Infection. Rieta Hough, M.D., San Diego. (By invitation.)

Report of case of *Penicillium glaucum* infection in a two-and-one-half-year-old girl, beginning in November, 1936, and ending in death April 25, 1937. The course was stormy with superimposed hemolytic streptococcus infection. Ethyl iodide inhalations produced temporary improvement.

### NOVEMBER 5

## Care of Skin of the Newborn: Prevention of Infection. L. Howard Smith, M.D., Portland.

Author's experience in treating 1,683 successive newborn babies by nonoiling and nonbathing is given. The vernix was not removed and skin not touched, except for the use of warm water on diaper region. Only two cases of suspicious pyodermia were observed. The advantages of the method are the lessened handling of the babies, the saving in nursing time, and the lessened incidence of skin infections. In the discussion Bonar advised the use of flexible collodion on the blebs. Grulee had applied the same treatment to premature infants with satisfactory results.

### The Undescended Testicle. Norman Nixon, M.D., Los Angeles.

The author had treated 59 cases of true cryptorchidism in boys aged two and one-half to fourteen and one-half years. In one-third of the boys, descent of the testes resulted. Treatment consisted of 250 rat units intramuscularly three times a week for 30 injections. Then after a rest of three months a second course was given. In half of the cases acceleration of genital development was observed. In 17 of 37 failures, operation was done. Previous endocrine treatment made surgery easier.

The Present Status of Endocrinology as Related to Pediatrics. E. Kost Shelton, M.D., Los Angeles (By Invitation).

A review of endocrinology as related to pediatrics was given and will be published in full in JOURNAL OF PEDIATRICS.

Convalescent Serum, Its Uses and Preparation. C. M. Hyland, M.D., Los Angeles. (By invitation.)

- 1. Measles: 423 cases of contacts treated—72 per cent prevented; 25 per cent modified; 3 per cent given too late in exposure. 2,344 susceptible contacts collected from literature—67 per cent prevented; 28 per cent modified; 3.6 per cent developed measles with no deaths.
- 2. Scarlet fever: 242 contacts treated—96.6 per cent prevented; 2.4 per cent developed mild attenuated disease. One hundred cases of scarlet fever treated: 19 per cent developed complications, which is less than one-half of nontreated cases. Attenuation of disease noted in treated cases; also used in nonscarlet streptococcus infections.
- 3. Poliomyelitis: Speaker urged larger doses in treatment, according to the work of Levinson.

Growth and Development as Related to Pediatric Surgery. Herbert E. Coe, M.D., Seattle.

Various congenital defects may interfere with normal growth and development. Among these are syndactylism, congenital dislocation of hip, torticollis, hypospadias, congenitally deformed ears, harelip. Among acquired conditions are muscle transplantations, osteomyelitis, hemangiomas, and burn scars which may interfere with normal growth and development.

The Course of Asthmatic Children in the Southwest. Vivian Tappan, M.D., Tucson.

The results of transplanting asthmatic children to Arizona climate were favorable on the whole. The group with respiratory infections, chiefly sinusitis, and who were not highly allergic, did best. The results in the markedly sensitive children were not as good. Infections in sinuses and in the bronchial tract present in majority and these seemed benefited. The longer the stay, the more marked the improvement. After returning to home environment improvement was maintained in the majority after interval of six months to six years.

Results of Eight Years' Treatment of Epilepsy in Children. Howard Cooder, M.D.,
Los Angeles. (By invitation.)

Total cases received for treatment in eight years

Number of cases treated one year or more

Cases with possible organic cause

Cases without organic evidence (idiopathic)

144

412

25

144

Length of time treated: Time free of attacks at last visit: 1 vr. 54 cases 1 yr. 2 yr. 48 cases 60 cases 2 yr. 3 yr, 27 cases 28 cases 3 yr. 3 cases 4 yr. 14 cases 4 yr. 5 yr. and up 13 cases 4 cases 5 yr. and up 1 case 169 cases Total free of attacks 1 yr. + S3 cases

Kind of treatment and results:

			Tring or treatment and result.			
Total stopped 1 yr. or mor	re 83	48%		2	.03	%
Total improved	53	31%	Diet only		23	
Total stationary condition	27	16%	Diet cured	21		
Total worse	3		Phenobarbital only		31	
Total died	3	5%	Phenobarbital cured	24		
			Diet and phenobarbital		115	
	169	100%	Diet and phenobarbital	38		
Relapsed after 1 yr. free	6 65	1505	cured			
•				<b>S</b> 3	169	48%
			Boarding home	17	cases	

Some Observations on the Results of Direct Blood Transfusions. Alonzo Cass, M.D., Los Angeles (By invitation).

A study was made of 270 cases of direct blood transfusions in the Children's Hospital, Los Angeles. The majority were given in cases of pneumonia, blood dyscrasias, and gastrointestinal disturbances.

Conclusion: Transfusion may be a bone marrow depressant and is not unassociated with danger in pneumonia and in critically ill children.

Encephalography in Children. Harry Dietrich, M.D., Los Angeles (By invitation).

Indications and contraindications for use of encephalography were given with illustrative cases shown in x rays.

### NOVEMBER 6

Additional Uses for the Oxcillatocapacigraph. Barnet E. Bonar, M.D., and Con Fenning, M.D., Salt Lake City.

The instrument, which has been devised by Penning to record graphically changes in volume or capacity of structures, was described briefly. Tracings were shown of the uterine activity and fetal activity, including fetal respiratory movements through the opened and unopened abdomens of experimental animals whose spinal cords had been transected. Records of cardiac movements of rat fetuses and turtles were shown as well as tetanic contractions of the skeletal muscles of the frog. The instrument has additional uses which can be applied to physiologic activity in humans, making it possible to record as many as four or five more or less synchronous movements at the same time with ease. Tracings were shown of Braxton Hicks contractions in the human, as well as respiratory activity, apex pulsation, neck pulsation and fontanel pulsation in a two month old infant. It is concluded that this instrument may be of value in making studies of human physiologic activity where ordinary methods now in use would be difficult or impractical.

Treatment of Adult Type of Pulmonary Tuberculosis in Childhood. Lloyd B. Dickey, M.D., San Francisco.

Notes on Therapy in Communicable Diseases. Paul M. Hamilton, M.D., Alhambra.

- Diphtheritic invocarditis: Treatment consisted of parenteral injections of glucose with sufficient pitressin to hold systolic blood pressure near a low normal level. Importance of frequent blood pressure readings emphasized.
- Scarlet fever: Dramatic improvement following use of convalescent human serum. Complication rate 9 per cent as compared with previous five year rate of 35 per cent.

- 3. Typhoid fever: 95 cases treated with intravenous bacteriophage. This method is still under investigation and is not yet recommended for general use.
- 4. Tetanus: Use of large doses, usually 200,000 units recommended with but 6 deaths in 44 cases. These studies made at the contagious disease hospital, Los Angeles General Hospital.

Intestinal Allergy. Phillip E. Rothman, M.D., and Helen Hopkins, M.D., Los Angeles (By invitation).

Clinically, the cases fall into two general groups: the first is characterized chiefly by a persistent diarrhea, and the second by gastric retention. Associated with these disturbances are a failure to gain weight, increased susceptibility to respiratory infections, and an alteration in desposition. Eczema, asthma, hay fever, or urticaria is rarely present. The diarrhea with marked abdominal distention may closely simulate celiac disease. Intestinal parasites and a functional colitis should be excluded in the differential diagnosis. The second group with vomiting as a predominating symptom may be confused with a congenital organic intestinal obstruction. The authors have had excellent results with the elimination of those foods producing positive skin reactions and believe that they are justified in ascribing the disorder to an allergic etiology.

Wood Tick Paralysis in Children (Motion Picture Demonstration). E. J. Barnett, M.D., Spokane.

Picture taken from cases reported in the Journal of the American Medical Association, September 11, 1937.

### Academy News

The following physicians have been elected to Fellowship in the Academy:

REGION I

John Giblin, New York, N. Y. Julius Margolis, Coatesville, Pa. Harold R. Mixsell, New York, N. Y.

REGION II

Hillard W. Willis, Coral Gables, Fla.

REGION 111

James J. Donahue, E. St. Louis, Ill. Harold O. Lund, Middletown, Ohio John W. Maroney, Detroit, Mich. Mark F. Osterlin, Traverse City, Mich. Thomas P. Saltiel, Chicago, Ill. Clara D. Tigay, Chicago, Ill. Dwight A. Weir, Mansfield, Ohio.

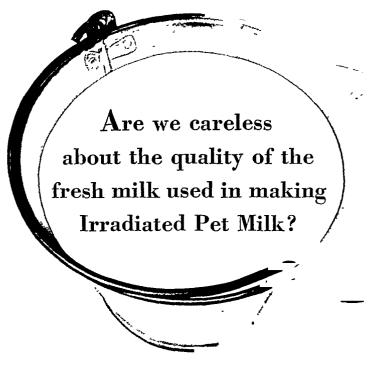
## Comments

THE decision of the executive committee of the Academy to change the 1939 annual meeting from the spring to the fall of that year, as reported in the minutes of their meeting in the JOURNAL last month (p. 131), is a wise change in our opinion. It implies a separation of the Academy meeting from that of the Section on Pediatrics of the American Medical Association. The American Medical Association has felt that the many meetings held in conjunction with their annual session has resulted in the many tails wagging the dog. On the other hand, many Academy members have felt that unless the two meetings were held close together, the attendance of pediatricians at the Section on Pediatrics would be cut down.

By changing the annual meeting to October, the Academy of Pediatrics falls in line with other large specialist groups as the College of Physicians and Academy of Otolaryngology. From the standpoint of being away from home and practice October is the best month for the pediatrician. The change further does away with the difficulty that has been encountered in securing suitable and adequate hotel facilities and with problems connected with the Academy exhibits.

THE Editorial Board of the JOURNAL feels it necessary once more to call attention to the problem of case reports submitted for publication. Only a limited number can be published in the JOURNAL; and hence many submitted must necessarily be returned to the authors. A case report to be accepted must contribute something to our knowledge of the condition described. Simple rarity or infrequency with which a condition has been described in literature only occasionally makes a case report worthy of permanent record in medical literature. It is not unusual for a case report to be submitted on the basis that the author has been able to find the condition reported but ten or twenty times in medical literature. Frequently to the knowledge of the Editorial Board many more cases have been seen and are in the records of our larger children's clinics, but have never been reported for the reason that nothing has been found in their study which has added to our previous knowledge of the condition.

While on this topic we might add that there is a tendency on the part of many authors to so overload a manuscript with unessential irrelevant details that the paper loses interest and force, and hence fails to register its points. We are certain that by careful rewriting many manuscripts submitted to the Journal could be cut from two to three out of every ten pages, and thereby would gain both strength and clarity.



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Official Organ for
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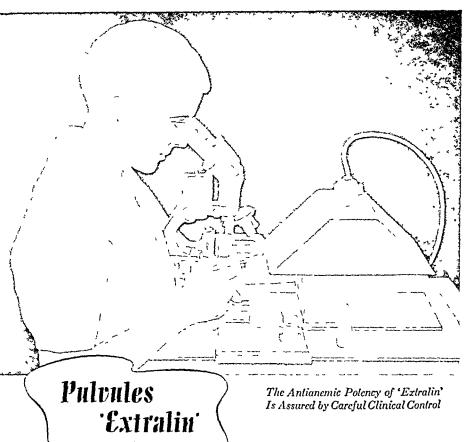
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\*Frazer, J. G.: The Golden Bough, vol. 1, New York, Macmillan & Co., 1923



It is ironical that the practice of attempting to cure rickets by holding the child in the cleft of an ash tree was associated with the rising of the sun, the light of which we now know is in itself one of Nature's specifics.

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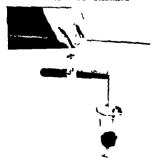
CURD OF FRESH COW'S MILK



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CURD OF BREAST MILK

## CURD formed during gastric digestion

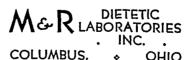
### MAY ALTER MOST CAREFULLY BALANCED FORMULA FOR INFANT FEEDING

When tough casein curds are formed in the infant's stomach only the surfaces of the curd are exposed to the digestive enzymes. Portions of the food substances are encased within the curd and are not utilized.\* Thus the feeding formula, though it may have closely approximated the composition breast milk, is prevented from supplying the necessary food substances in the proportions intended.

> \*See Morse & Talbot: Diseases of Nutrition and Infant Feeding, pp. 48, 59, 61, 214, 215.

At the right are actual photographs of cow's milk, powdered whole milk, Similac, and breast milk, after the addition of essence of pepsin. Note that only breast milk and SIMILAC are physically unaffected by the coagulant while the other milks have formed a curd. Both breast milk and SIMILAG have a consistently zero curd tension. Since SIMILAC does not form a curd the digestive enzymes act upon it quickly and thoroughly, making available for metabolism all of the food substances included in the formula. Because of this fact SIMILAC has

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> Friedenwold and Ruhrah "Diet in Health and Disease"

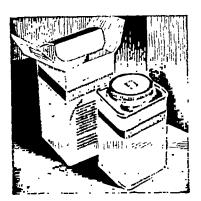
A-Without gel atine, bard, in digestible milk curdi

B-With gelatine soft, flocculent milk curds



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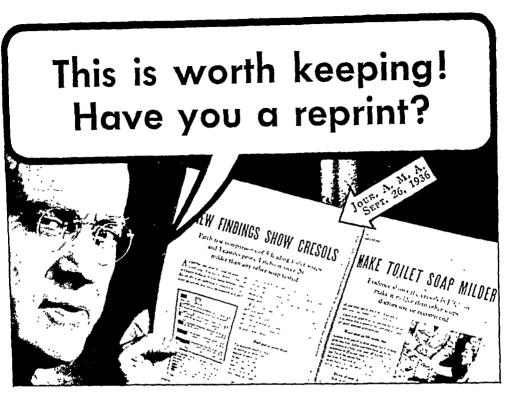
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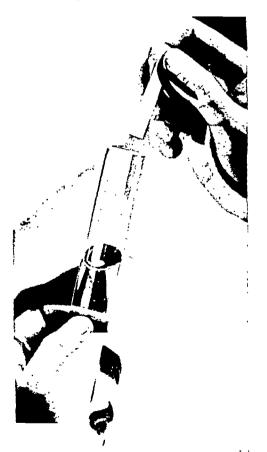
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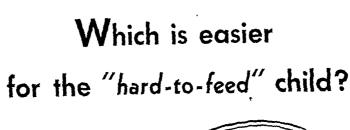
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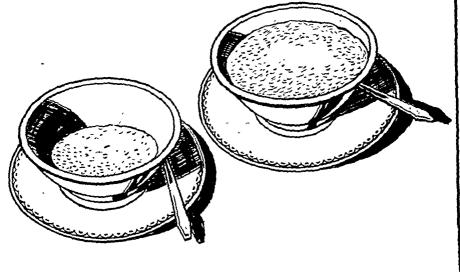
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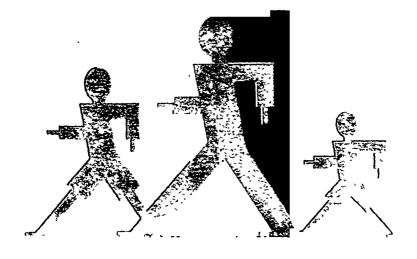




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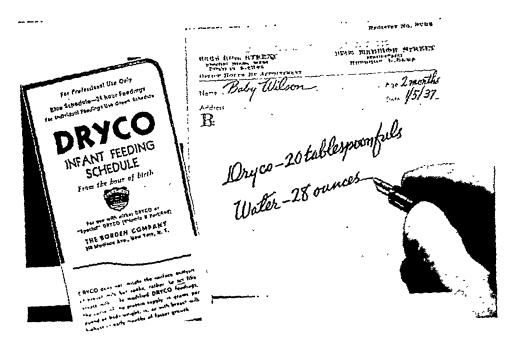


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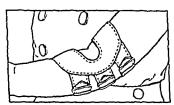
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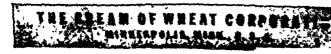
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By Frederic W. Schlutz, M.D., Minerva Morse, Ph.D., and Helen Oldham, Chicago, III.

ATRESIA OF THE PULMONARY ORIFICE WITH INTACT INTERVENTRICULAR SEPTUM. By Matthew M. Steiner, M.D., Brooklyn, N. Y.

A SHIFT IN THE INFANT MORTALITY RATE IN DURHAM COUNTY, NORTH CAROLINA. By Jeremiah W. Kerner, M.D., Durham, N. C.

TYPHOID FEVER IN CHILDREN.

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ENDOCRINE OBESITY IN CHILDREN: CLINICAL AND LABORATORY STUDIES AND RESULTS OF TREATMENT.

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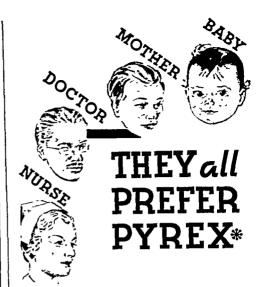
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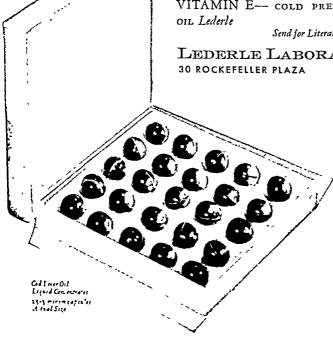
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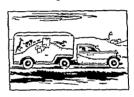
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### The Journal of Pediatrics

Vol. 10 January, 1937

No. 1

### Original Communications

### DYSCHONDROPLASIA

Howard R. Mahorner, M.D. New Orleans, La.

ULTIPLE bony prominences have been known to occur on the M skeleton of certain individuals since olden times. According to Reinecke, Stanley first recorded the familial tendency in 1849. There are an increasing number of papers relative to the subject, particularly concerning the clinical and roentgenologic characteristics of the affection and the prevalence of this particular type of osseous dystrophy; yet it is still generally considered to be rare, and a lack of familiarity with the disease is the rule. Etiology of the disease and therapy are still unpenetrated fields. Also confusing is the question of terminology and classification. Such a variety of terms have been used to designate the condition that one selects the name most appealing to him, or invents a new one. Some of these are: hereditary multiple exostoses (Gibney, 1876); multiple exostoses (Gibney, 1879); multiple cancellous exostoses (Davis4 and Vaughu5); multiple cartilaginous exostoses (Ashurst<sup>6</sup> and Lewin<sup>7</sup>); multiplen Wachstumsexostosen (Reinecke<sup>1</sup>); dyschondroplasia (Ollier<sup>8</sup>); chondrodysplasia (Dwyer, Ocle, o and Cleveland); diaphyseal aclasia (Keith); hereditary deforming chondrodysplasia (Ehrenfried<sup>13</sup>); multiple congenital osteochondromas (Boggs,14 and Carman and Fisher15); Ollier's disease (Richard, Dupuis, Roederer, and Froyez<sup>16</sup>, and Hunter and Wiles<sup>17</sup>); familial deforming chondrodysplasia (Gorsline<sup>18</sup>); multiple cartilaginous enchondroses (Haas<sup>19</sup>); and familial chondrodystrophy (Hilton<sup>20</sup>).

Classification.—The individuality of the condition and its relationship to other developmental anomalies affecting the skeleton is still subject to question. In 1898 Ollier<sup>21</sup> recorded a single case of bilateral multiple exostoses which he had seen in a beggar in Egypt. In 1899 he<sup>8</sup> called attention to a condition which he named dyschondroplasia. He had seen four cases, one a case of multiple exostoses in a child some years before this, the records of which were lost. The second case

From the Department of Surgery, Tulane University School of Medicine, and the Surgical Clinic, Hutchinson Memorial Clinic.

was in a child six and a half years old who had a curved right forearm, exostoses on the right femur, and shortness of the upper and lower extremities on the right side only. X-rays taken when the child was seven and a half years of age showed incomplete ossification of the metaphyses. A third case similar to the others occurred in a girl nine years of age, except that both sides were equally affected. He observed a fourth case in a girl thirteen years of age. The long bones of one side only were affected, but both hands were involved. Olliers concludes that one would judge that the lesion of the long bones is unilateral. He did not mention in his second paper the beggar he described in 1898, but he did say that dyschondroplasia was related to osteogenic exostoses.

The influence of Ollier's paper has been extensive. He showed by x-rays which had not long been available for clinical use at the time, that in cases with multiple exostoses there is another finding more fundamental; viz., incomplete areas of ossification of the metaphyses, clear areas in the juxtaepiphyseal portions of the long bones. found by biopsy that the clear areas in the phalanges were due to cartilaginous masses, described the underlying pathology more accurately, and named the condition "dyschondroplasia." a term calling attention to the fundamental lesion, a disturbance in the growth of the epiphyseal cartilage, and ossification of the metaphyses. But to von Bergmann must be given, according to Frangenheim<sup>22</sup> and others, 23, 24, 4, 14 the credit of first attributing the cause to a disturbance in the epiphyseal cartilage. The confusing part about Ollier's8 report is that he regarded one characteristic of the affection as unilaterality or thought that involvement of the larger bones is unilateral. However, the first and third cases in his second paper8 may not have been bilateral. He says that dyschondroplasia is similar to osteogenic exostoses. Since certain authors (Cole, 10 Hunter and Wiles 17) have regarded unilateral dwarfing with multiple exostoses affecting one side as an individual clinical entity, separate from generalized multiple exostoses, a controversy exists as to the relationship of the two conditions. Most authors regard them as the same disease (Frangenheim,22 Ehrenfried,13,25 Jansen26). Molin,27 a student at Lyon, published his thesis on dyschondroplasia in 1900. He reported four eases, all of which had an asymmetrical unilateral involvement, except one which had the left upper and the right lower extremity involved. Subsequent studies show that such dystrophies affecting only one side are much less common than similar eases in which both sides are involved. Ollier's apparently may have attempted to emphasize the unilateral case as the true type of what he called dyschondroplasia. In two of the most important contributions to the subject, Ehrenfried, 13, 25 in 1915 and in 1917, called attention to the prevalence of cases of multiple exostoses and emphasized the hereditary basis which could be proved in a large percentage of instances. Removing a specimen from an area crossing the epiphyseal line, he found a dysplasia of cartilage cells of the epiphyses. He described the general clinical and roent-genologic characteristics of the disease, included disseminated and unilateral cases, and chose to use the name "hereditary deforming chondrodysplasia," which because of his articles has become a popular name for the disease in this country. He regarded the bilateral cases and the unilateral cases as the same disease.

In 1915 Albers-Schönberg<sup>28</sup> described a hitherto unrecorded type of skeletal dystrophy characterized by roentgenologic appearance in the bones of rounded or irregular areas 2 mm. to 5 cm. in diameter, which were more opaque to x-rays, areas he thought of condensation of calcification. The diaphyses of long bones were not involved, but the metaphyses and epiphyses were. The only bones that were entirely free of the appearance were vertebrae, skull, scapulas, and patellas. There was a suggestion of exostosis on one humerus. He regarded the affection as a developmental defect. In viewing Albers-Schönberg's plates, a suggestive broadness of the metaphyseal region of the long bones is noted, a finding, if true, which even more decisively puts this ease in the class of dystrophies under discussion. The exostosis is quite definite.

Voorhoeve,<sup>29</sup> in 1924, reported findings in a brother and sister, aged fourteen and ten years, respectively, in which the principal findings were longitudinal striations in the bones, especially in the juxtaepiphyseal regions. These very definite straight striations were not due so much to increased density as to incomplete ossification along alternate lines. The densest areas had approximately the same density as the middiaphyseal regions which were apparently normal. On the other hand, the areas of condensation in Albers-Schönberg's case28 were more dense than normal. In Voorhoeve's20 cases the broadness of the metaphyses extended an abnormal distance up the shaft, and small exostoses were found in the metaphyseal regions. Voorhoeve29 believed that his cases and Albers-Schönberg's case28 are types of dyschondroplasia. Fairbank30 reported a case of a boy aged twelve years with roentgenologic findings which are almost identical with those of Voorhoeve's cases.29 The lower extremity on the left side in Fairbank's case30 is shorter than that of the opposite side which fact is further evidence that the type of dystrophy is related to that described by Ollier.8 Fairbank<sup>30</sup> did not know the disease he described. He quotes Bentzon,31 but not Voorhoeve.29 Bentzon's case31 resembled the type described by Voorhoeve.29 A case similar to that reported by Albers-Schönberg2s has not been found recorded, and this extreme rarity, together with the fact that the stippling found in the hereditary deforming chondrodysplasia type of dyschondroplasia is usually not due to an increased density but to an incomplete ossification in surrounding areas, weakens the conclusion that Albers-Schönberg's case<sup>28</sup> is a type of dyschondroplasia. However, the juxtaepiphyseal distribution, broad metaphyses, and exostosis leave little doubt that it is related to dyschondroplasia.

Freund's reported a case which he called "osteodystrophia fibrosa unilateralis." which he believed to be related to Ollier's dyschondrophasia. Freund's case<sup>32</sup> was unilateral with facial asymmetry, but the whole diaphysis as well as the metaphyses of the long bones was affected. There was a diffuse osteoporosis without cyst formation. Biopsy showed the haversean canals to be enlarged by osteoclastic resorption, and so suggestive were some of the appearances of osteitis fibrosa cystica that the patient was explored for a parathyroid tumor. This condition is not included in the classification by the author because the principal lesion was not in the metaphyses.

Cole<sup>10</sup> in 1926 believed that the term "Ollier's disease" should be reserved for those cases of eartilaginous dystrophy which show an asymmetrical involvement of the skeleton. Hunter and Wiles17 attempted to differentiate Ollier's dyschondroplasia from hereditary deforming chondrodysplasia on the basis of four features. hereditary deforming chondrodysplasia heredity is a striking finding, whereas in Ollier's type of dyschondroplasia heredity is infrequently proved. Second, enchondromas are almost invariably in the former. They may occur in the latter but are not so frequently found. broad metaphysis is constant in hereditary deforming chondrodysplasia but, according to them, not in Ollier's dyschondroplasia. Fourth, they say there is fairly regular calcification giving homogenous roentgen shadow to the bone in hereditary deforming chondrodysplasia. Differences undoubtedly occur in the two conditions, but they are relative. Unquestionably in the unilateral and bilateral cases incompletely ossified areas occur in the juxtaepiphyseal areas, osteochondromas occur, and restricted growth of the affected bones is found. It is true that the unilateral cases are likely to be sporadic in which heredity cannot be demonstrated, but in some bilateral cases heredity cannot be proved. Exostoses seem to be more numerous and more prominent in the bilateral cases. In both, the broadness of the metaphyses extends over a greater portion of the bones than the normal metaphysis even if this is relatively more pronounced, as Hunter and Wiles17 maintain, in the bilateral type. One who has carefully studied the pictures presented by ('oon' of a boy fifteen years of age who had the disease will forever distrust the strict unilaterality of the disease in any cases not proved by complete x-ray films of the skele-The clinical picture shows the short right arm and leg, and

roentgenograms of this side reveal the unmistakable findings of Ollier's type of dyschondroplasia. Roentgenograms of the opposite side also disclose signs of the disease, though not so pronounced. On the side apparently not affected in the clinical picture of the patient, the roentgenograms show longitudinal striation, abnormal curvature, small exostoses, and other manifestations of involvement.

Even without a history of occurrence of the disease in a family, it is questionable whether multiple exostoses occurring in an individual can be differentiated as a distinct entity from dyschondroplasia of the hereditary deforming chondrodysplasia type. Sporadic single exostoses on a skeleton are not to be classed with this disease, but multiple exostoses occurring in a single individual of a family can be shown to have the characteristics of dyschondroplasia. They affect mainly the metaphyses of long bones and show other evidences that definitely put them in this class. Because dyschondroplasia can be latent, it is difficult to definitely prove that heredity is not a possibility.

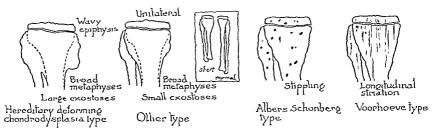


Fig. 1.--Diagrammatic representation of four different types of dyschondroplasia showing the predominating x-ray characteristics of each type.

Because all these conditions affect the bones mainly in the juxtaepiphyseal regions, are developed during the growth period, and are characterized by disturbances in cartilaginous growth, ossification, and failure of proper diaphyseal formation (lack of resorption and remodelling of the metaphyses), the author prefers to call them all dyschondroplasia and designate them as four main types (Fig. 1) in which one or another characteristic predominates:

### Dyschondroplasia

- Ollier's type (unilaterality).
- 2. Hereditary deforming chondrodysplasia (Ehrenfried) type, many exostoses, broad metaphyses, heredity frequently proved.
- 3. Voorhoeve's type. Longitudinal striation of metaphyses is the most prominent feature.
- 4. Albers-Schönberg's type. Areas of increased density in the metaphyses and epiphyses are the most prominent features.

Incidence.—In 9.442 admissions to the Hutchinson Memorial Clinic of Tulane University there have been five cases of dyschondroplasia (hereditary deforming chondrodysplasia type), three cases of achon-

droplasia, one case of hyperteliorism with dwarfing, and six cases showing single exostoses. There have been no cases of Morquio's disease, no cases of osteogenesis imperfecta, hyperchondroplasia, Madelung's deformity, or aplasia of an extremity. There has come under my care another case of dyschondroplasia of the hereditary deforming dyschondroplasia type, an abortive form discovered in a child who

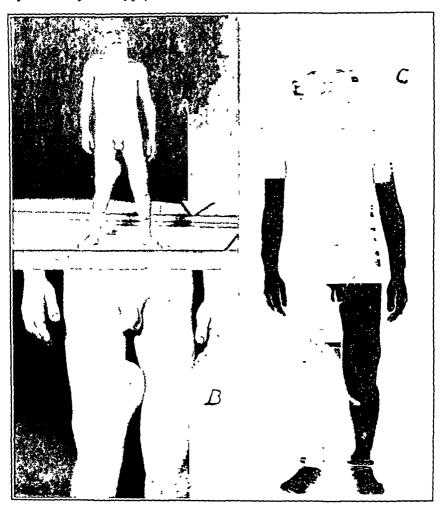


Fig. 2.—.1 and B, Case 1, before operation, showing the bony prominences and deformities mentioned in the text. C, After removal of osteochondroma from femur. Note pronution of hands, marked irregularity in growth of bones, and the prominences (exostoses) near the ends of the long bones. The patient is of short stature.

was x-rayed because of fracture. The only evidence of the disease in this case was deficiency in growth of the terminal end of the ulna with a pointed tip and broad metaphysis resulting in the typical arrowhead deformity. This appearance is so characteristic that it is unmistakably dyschondroplasia.

#### CASE REPORTS

CASE 1.—E. B., No. 7083, white male, aged twelve and one-half years, with hard, painless, irregular masses attached to the long bones of the extremities and other bones of the body. The masses were first noted in infancy; the exact date of their appearance could not be determined. Beginning as small lumps on the bones in the region of the joints, they gradually increased in size. One mass on the inner mesial aspect of the right femur had grown in size more rapidly than the others until now it is the size of a grapefruit and interferes with his walking (Fig. 2.) He had failed to grow in height properly. His father and other members of his family were affected (Chart 1), and it was noted that those members of the family affected on reaching full growth were of short stature (height 5 feet 1 or 2 inches), whereas other members of the family who were not affected were all taller. Exami-

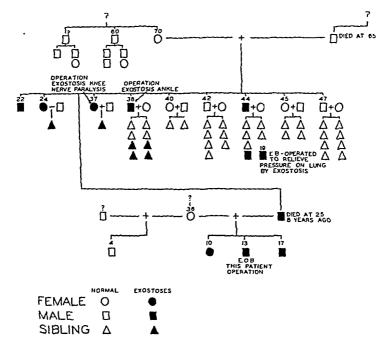


Chart 1.—Showing the incidence of dyschondroplasia (hereditary deforming chondrodysplasia type) in the family of patient in Case 1. Of fifty-two members excluding ten mates of two generations of the family, seventeen (one-third) had the disease.

nation revealed a well-nourished, well-developed, intelligent boy, stubby but with good musculature. He walked with a waddling gait in order to clear a large mass projecting messally from the lower end of the right femur. Valgus deformity of the right knee and varus deformity of the left were noted on standing. There were numerous exostoses of the extremities near the ends of the long bones, especially marked at the lower end of the femurs, upper ends of the tibias, the lower ends of the radii and ulnas, and the proximal ends of the humeri. Supination of each forearm was limited 45 degrees. There were numerous small exostoses on the hands and feet. The spine and skull and bones of the face showed no abnormalities, but the nasal septum, which was abnormally broad and cartilaginous, encroached on each nir passage. The scapulae and pelvis were not clinically involved, nor were the ribs.

Laboratory findings included leucocytes, 10,000 per cubic millimeter; eosinophiles, 14 per cent; strongyloides in the stool, and urine negative.

Roentgenograms of Right Forearm and Hand.—In the lower third of the radius and ulna jutting into the interoseous space are moderate-sized osteomas that abut on each other. Apparently there is no fusion between the two. The bones are separated and the interoseous space is wider than normal. A small evostosis arises from the distal metaphysis of the radius on the outer side, and this together with the normal metaphysis makes the juxtaepiphyseal portion of the bone wider than the epiphysis. The distal end of the ulna is not pointed and shows no exostosis. The metaphyses are irregularly and insufficiently calcified, with the result that transverse and longitudinal trabeculation stands out. The left forearm shows similar changes, but they are more exaggerated. An irregular bony projection arises from each bone

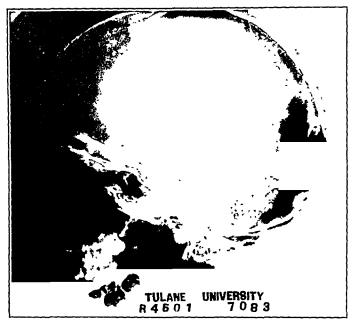


Fig. 2.—X-ray film of skull in Case 1 shows pregular calcification, a finely mottled appearance.

at the distal end and is directed into the interesseous space. The distal end of the ulna is pointed, and there is a very small epiphysis. The epiphyseal line of the radius is curved and irregular.

Metacarpals of both hands show insufficient calcification at the juxtaepiphyseal regions, and there are several small irregular exostoses originating from metaphyseal regions. The fourth and especially the fifth metacarpals of the left hand are relatively short when compared with the second and third. Also the head of the os magnum is disproportionately large when compared with the body of the bone.

Roentgenograms of the skull show an indistinct, furry, irregular type of calcification (Fig. 3).

Roentgenograms of the lower femurs, knees, and upper part of the tibias show on the medial aspect of the right femur a large bony mass with a broad base, no visible cortex, and treelike radiating calcification (Fig. 4). The base is approximately as wide as the diameter of the wide metaphysis at this level, and the diameter

and width of the mass is slightly greater than this. The right tibia is curved concave outward in the upper third. The metaphysis of the tibias and femure show the broadness of the epiphysis extending for an abnormal distance on the diaphysis, and there is irregular, insufficient calcification and thin cortex. A few other very small exostoses are seen. The fibula heads are large and are poorly calcified. These insufficiently calcified areas show streaking and stippling, an abnormality which seems to involve also the epiphysis proper. The epiphyseal lines are slightly irregular.

The large osteocartilaginous mass on the mesial aspect of the right femur was removed on March 12, 1935, under general anesthesia. The entire capsule and part of the attached muscles were removed with it in order to avoid detaching cartilaginous or bone-forming elements that would favor a recurrence. It was noted at the time



Fig. 4.—Roentgenogram of knees in Case 1. The large esteema is evident in the lower end of the right femur. Note the irregular calcification of the metaphysis and the broadness of the metaphysis due to failure of diaphysation. The epiphyseal lines are wavy and the right tibla is curved.

the base was being chiseled from the shaft of the femur that it was very soft, not uniformly ossified. The mass measured  $9\times 9$  cm. It was covered by a soft cartilaginous capsule. The central portion showed numerous hard, bony trabeculae, and a yellowish surface which had an oily moisture.

Sections were taken from the surface, the central part of the mass, and the center of the pedicle (Fig. 5). Microscopic examination of slides prepared from these showed on the surface the connective tissue capsule, a thin fibrous perichondrium beneath which was cartilage with moderate-sized cartilage cells. These cells became larger in the deeper portion of this cartilaginous cap. The cartilaginous

zone showed absolutely no evidence of ossification. It stopped abruptly and subjacent to it was a zone of cancellous bone, a few bony trabeculae, no compact bone. Red marrow is found between the trabeculae. In the deeper areas are trabeculae of cancellous bone, in the interstices of which is found fat and occasionally some few marrow cells.

CASE 2.—J. R., No. 3022, negro male, aged eighteen years, had had since infancy abnormal bony prominences noticeable at the right humerus below the insertion of the deltoid and near the knees. There was no family history of a similar affection. He came because the mass on the right humerus had been rapidly increasing in size.

Examination revealed a well-nourished, well-developed young negro. There were abnormal, irregular, bony prominences projecting from the long bones near the knees and at the upper end of the right humerus a well-developed mass,  $8 \times 6$  cm., firmly fixed to the bones.

The laboratory findings showed hemoglobin, 95 per cent; erythrocytes, 5,255,000; leucocytes, 6,250; urinalysis, negative.

Rocatgenograms of the Knees.—The broad part of the metaphysis of the femur extends well up the shaft (Fig. 64). The cortex is thin, and there is some evidence

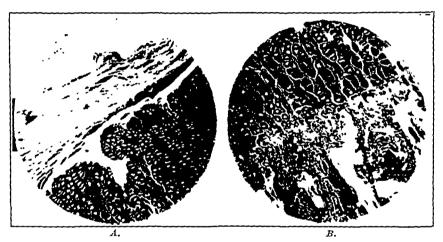


Fig. 5.—A, Microscopic section of cortex of osteoma removed from Case 1. There is no evidence of ossification. No osteoblasts invading from the surrounding fibrous tissues.

B, Deeper section at junction of cortex and medulla showing the large cartilage cells and abrupt change to spongy bone beneath. There are a few osteoblasts and no evidence of calcification of the matrix of the cartilage which should normally occur as a groundwork for bone formation.

of longitudinal striation and stippling. Sharp pointed exostoses project upward from each femur at the junction of the shaft and metaphysis. Several small exostoses project from the metaphysis of the tibia. The same evidences of incomplete calcification are present. The head of the fibula on the left has definitely fused with the tibia. It is irregular, but no exostoses are seen on its lateral side. The interosseous space is wide and gives the appearance that the head of the fibula was pushed away from the tibia. In the head of the right tibia similar changes are found, but they are less marked. The epiphyseal lines of the tibias and femurs are faintly visible. Their contours appear regular.

The upper end of the right humerus shows several exostoses at the junction of the middle and upper thirds. One is large with a length as great as the diameter of the shaft. It points outward and downward (Fig. 6B).

No other x-ray plates were taken.

The patient refused to have the exostosis removed from the humerus.

Case 3 .- H. H., No. 8003, white male, aged eight years. When aged three years, he was observed by the parents to have a small, abnormal, bony projection just below the right knee. It increased in size and within two years had again entirely disappeared. When he was five years of age, nodules were noted in the region of the knees, wrists, shoulders, fingers, and these have progressively increased in size until when at the age of eight years, when he was examined at the clinic, they were numerous and varied from the size of a small marble to that of a golf ball.

Examination revealed a well-developed and well-nourished boy, height 511/2 inches. In the region of the ends of the long bones of the extremities were firm, irregular projections, painless and attached to bone, but subcutaneous and unattached to Knees, wrists, elbows, shoulders, scapulae, humeri, and ribs had exostoses. The head, face, and spine were uninvolved.

Roentgenograms of the upper portion of left humerus and left side of chest show multiple exostoses in metaphyseal region of humerus. The metaphysis is broad

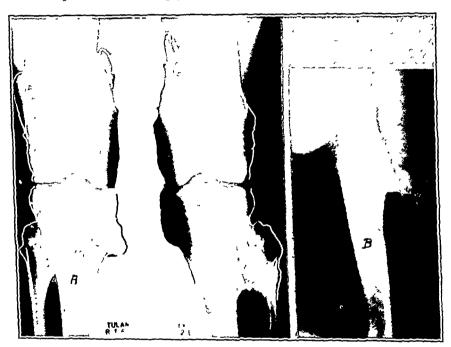


Fig 6.—Case 2. A, The roentgenograms have been retouched to preserve the outline of the bones. Numerous exostoses are seen pointing away from the epiphysis. There is fusion of the tibia and fibula and a broad metaphysis.

B, The sharp exostoses of the humerus point away from the adjacent epiphysis.

with a thin cortex. With the exostoses the metaphysis is broader than the normal appearing epiphysis. The epiphyseal line is irregular and not typically conical, Small exostoses are visible on the fourth left rib outside the angle and on the scapula.

Roentgenograms of the upper portion of right humerus and right side of chest show an expanded metaphyseal portion of the right humerus with several moderatesized exostoses and thin cortex. The coracoid process seems irregular, and there is an exostosis on the body of the scapula.

Lower ends of tibia and fibula: On the right the lower end of the fibula is curved concave inward. The epiphyseal line of the fibula is higher than normal, being on the level with that of the tibia (Fig. 7). The metaphysis of the fibula is wide for an abnormal distance up the shaft, and it is imperfectly ossified with a thin cortex. The epiphyscal line of the tibia is not straight across but is wavy, being higher

at one place than at another. Stippling or irregular calcification seems to be present in the metaphyses. On the left the lower end of the tibia as well as the fibula seems to be slightly curved. The metaphysis of the tibia is broad and slightly stippled, and the epiphyseal line is wayy.

Roentgenograms of knees: The tibial metaphyses are broad for some distance down the shaft, and there are longitudinal striations and stippling. One area is moderately deficient in calcification. The epiphyseal lines are wayy. The fibula heads show less perfect calcification. They are irregular in outline, and there are several exostoses, especially on the left, and these give the appearance of pointing up or toward their adjacent epiphyseal line, an unusual finding since osteochondromas, as a rule, have then apex directed away from the adjacent epiphysis. However, the exostoses in this instance are so small one cannot be sure of the direction. The width of the metaphyseal area is much greater than the relatively small epiphyseal

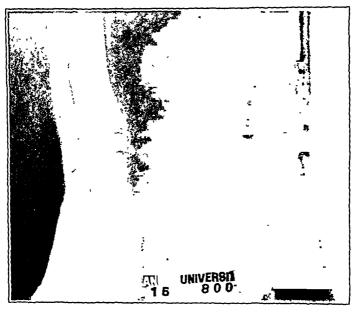


Fig. 7.—Case 3. The lower ends of the tibias and fibulas show irregular calcification with a wavy epiphyseal line. The cpiphysis on the fibula of the right leg is abnormally high, being on a level with that of the tibia, whereas normally it should be at the level of the joint. Curving of the tibia and fibula is noted.

line. The lower ends of the femure appear almost normal. There are several small spurlike exostoses pointing away from the epiphyseal line. There is a suggestion of streaking in ossification.

Roentgenegrams of hands and wrists (Fig. 8): The phalanges and metacarpals show what appear to be osteoporotic areas with a suggestion of linear streaking. There are no clear punched-out areas suggestive of enchondromas, but there are small exostoses. These tend to be near the epiphyseal lines; i.e., distal on the metacarpals, except the first; proximal on the phalanges and first metacarpals. The metacarpals are disproportionate in size, the fourth and fifth on each hand being relatively much shorter than the others. The right radius has an abnormally small epiphysis which is faced in on a curved epiphyseal line. The metaphysis of the radius is wider than the epiphysis, even that part of the metaphysis immediately adjacent to the epiphyseal line. A large irregular exostosis springing from the radius occupies the interesseous space and approaches a smaller one on the ulna. The inferior radio-

ulnar joint is widely separated. The epiphysis of the ulna is extremely small, and the metaphyses of the radius and ulna are incompletely ossified and have very thin cortices. Practically the same changes are found on the left side, but they are less marked. The distal metaphysis of the ulna here tends to be more pointed. The carpal bones show slight changes suggesting irregular calcification, and their forms are slightly bizarre.

Case 4.—W. A. H., No. 8004, white male, aged thirty-eight years, is the father of patient in Case 3. When he was two and one-hulf years old, his parents first noticed nodular prominences at the lower end of the femurs. When he was six years old, the nodules appeared about the elbows and at the lower angle of each scapula. Painless, they gradually increased in size. No increase in size of the tumors occurred after he was eighteen years of age. An exostosis was removed from the right os calcis when he was thirty-two years old, because it interfered with walking.

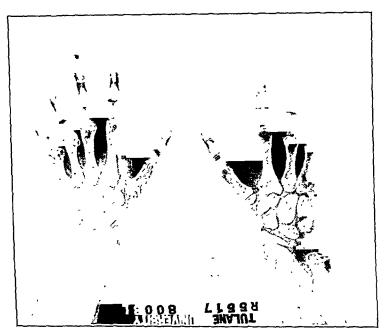


Fig. 8.—Case 3. There is irregular calcification of the bones of the hands and adjacent, part of the radius and ulna. The metacarpal bones are disproportionate in length, the fourth and fifth being relatively shorter than the others. Note that the small exostoses occur near the epiphyseal line. Some of the carpal bones are bizarre abnormal shapes. Each ulna is short. There is a false radio-ulnar joint on the right and failure of development of the epiphysis of the ulna on the right. The metaphysis of the radius in each instance is broader than the epiphysis.

He did not think that his parents or any of their relatives were similarly affected. One son had the disease, but three other children were unaffected.

Examination revealed a well-nourished, well-developed muscular white man, weight 200 pounds, 5 feet 5 inches in height. He had a waddling gait and knock knees (Fig. 9). The arms were carried in marked pronation with a varus deformity of the elbows. Multiple large exostoses were found on the entire ekcleton except the head and the spine. The ribs and scapulae are involved as well as the long bones of the extremities. The largest mass was found attached to the mesial side of the upper extremity of the right humerus, interfering with complete adduction.

Wassermann and precipitin tests were negative. Erythrocytes numbered 4,675,000, the hemoglobin estimation was 80 per cent and urinalysis was negative,

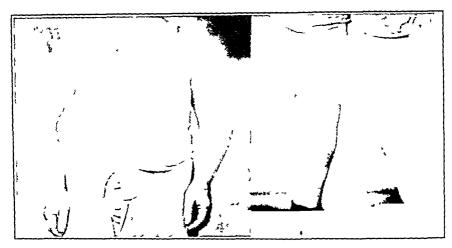


Fig 9—Case 1 This patient the father of patient described in Case 3, has dischondroplash of the hereditary deforming chondrod splasma trye. He has marked value of both clows and a dislocation of the head of the radius (Fig 10). Huge osteomy at the upper end of the right humerus interferes with the adduction of the arm (Fig 11). Note the valgus deformity of the knees which is a frequent finding Multiple evostoses not clearly shown were found in the region of the knees (Fig 12) (From Mihorner. South Surgeon 1936)

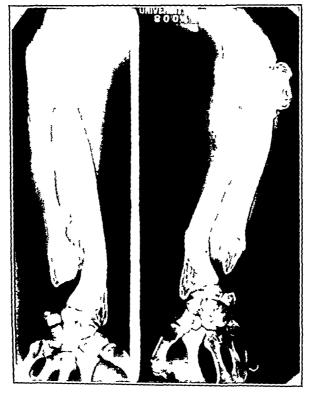


Fig. 10—Case 4. An excellent example of arrowhead deformity as seen at the district end of the left ular. The tip is pointed and the metaphysis is broad. The rulius is relatively much longer than the ular. It shows a dislocation at its upper and Aote the peculiar shape of the carpal bones. (From Mahorner. South Surgeon 1937.)

Roentgenograms.—Left forearm, wrist, and elbow: The radius is markedly bowed, relatively much longer than the ulna, and the head of the radius is dislocated (Fig. 10). The inferior articular surface of the radius faces toward the ulna. The interosseous space is vider than normal, and the lower end of the radius is widely separated from the ulna. The broadness of the metaphyses of the radius and ulna extends for an abnormal distance up the shaft. There is incomplete ossification of the metaphyses and several small exostoses on all metaphyses of each bone, more at the lower ends of the radius and ulna. The lower end of the ulna shows a most characteristic "arrowhead" deformity. It is pointed at the tip and broad in the metaphysis. Changes in the right radius and ulna are similar but not quite as marked. Dislocation of the head of the radius is plainly visible in the x-ray film, and another false head has formed below the true head.

Upper end of the humeri: The broad metaphyses extend one-third of the distance of the shaft. The cortex is thin in this area, and there is definite stippling

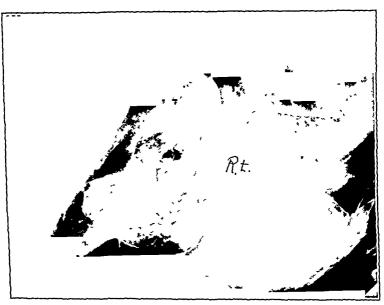


Fig 11.—Case 4, showing the huge osteoma at the upper end of the humerus which prevented adduction of the arm.

and a suggestion of longitudinal striation on the left. On the right the calcification has been irregular, in some areas patchy, and in some the striation tends to be transverse. A large ostcoma occupies the medial side of the upper third of the right humerus (Fig. 11). Its broad base and diameter are approximately the same as that of the broad metaphysis. A thin cortex and irregular calcification are likewise evident here.

Tibias and fibulas: There is a beautiful example of fusion of both fibulas and tibias at both the superior and inferior ends (Fig. 12). This bony fusion is present over a much larger area than the usual area of contact. The interosseous space is broader than normal. The metaphyses are broad with the usual thin cortex and irregular calcification. The middle shafts of the fibulas seem to be relatively larger, that of the tibias relatively smaller than normal so that the appearance suggests that both bones, instead of the tibia alone, are bearing the weight. This is actually true because of the deciation (valgus) at the ankle joint. The inferior articular surface of the tibia is not transverse to the long axis of the bone, but is deviated

from the normal 45 degrees so that the joint surface faces outward and downward. The fibula is short, but it is not because of this short fibula that valgus is present as some authors. In maintain. The valgus is due to deviation of the articular surface of the tibia, and the head of the fibula bears some weight from the upturned outer surface of the astragalus.

CASE 5.—A. R., female, aged thirty-four years, had a roentgenogram taken of both knees because of pain and swelling in the left with tenderness at the outer anterior aspect of the superior articular surface of the tibia, which pain was occasioned by a fall. There was no history of bone dystrophies in the family. The patient quickly recovered with a knee support and rest, but, though the roentgenogram showed no evidence of injury to the bone, it did disclose slightly prolonged metaphyses of the tibia and a pointed exostosis jutting downward from each metaphysis. X-ray plates of the wrist, which were taken with the expectation of possibly finding further evidence of dyschondroplasia, were negative.

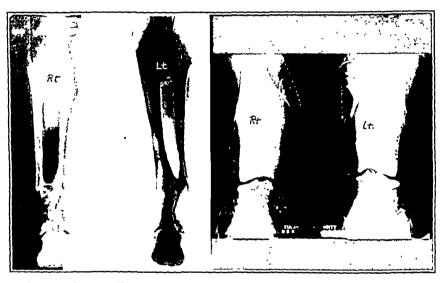


Fig. 12.—Case 4. There is fusion of each tibia and fibula at the upper and lower ends. The ankle joint is deviated outward, throwing some of the weight of the astragalus directly on the fibula. The shaft of the fibula is relatively broad compared with that of the tibia, which undoubtedly is due to the fact that the fibula has become a true, weight-bearing bone. The dotted lines shown on the roentgenograms of the knees indicate the limits through which ossification proceeded in the growth of bone. Absorption of part of this to form the diaphysis has occurred, but the exostoses remaining suggest that the purtial failure of diaphysation has resulted in abnormal bony prominences. On the left, however, the projection of that part of the exostosis beyond the dotted line cannot be accounted for by failure of diaphysation but must have resulted from abnormal growth. (From Mahorner: South, Surgeon, 1936.)

Case 6.— The author has had one additional case, the record of which is lost. The child had a fractured arm and in taking roentgenograms of the break, a peculiar condition was noted—failure of development of the distal end of the ulna resembling the appearance of the so-called "arrowhead deformity" found not infrequently in the hereditary deforming chondrodysplastic type. The distal ulnar epiphysis was poorly formed and the end pointed with the broad metaphysis and incomplete calcification. There were no other lesions. No other member of the family was known to be affected. This particular case, undoubtedly an abortive type of the condition, would probably have remained undiscovered had it not been for the fracture. It indicates how the disease may remain clinically latent and thus mask its hereditary basis.

### CLINICAL CHARACTERISTICS

Age of Onset.—The first manifestations of dyschondroplasia are generally noted by the parents in infancy or early childhood. The age of appearance was noted by Honeij<sup>34</sup> in 66 cases reported in the literature: At birth, I case; birth to five years, 12 cases; five to ten years, 7; ten to fifteen years, 4; fifteen to twenty years, 2; after twenty years, I. The remaining cases gave no information as to the time of first manifestations.

Davis says that Dreicher in 1889 and Reulos in 1885 described cases that were noted at birth. As a general rule, the affection is first noticed between eighteen months and five years of age, and sometimes later in life; some cases, being latent, are discovered only accidentally. Undoubtedly roentgenograms at birth would disclose indications of the disease in cases that are not clinically manifest until later.

Sex.—Males are more often affected than females. Reinecke<sup>1</sup> reports the ratio as 3 to 1, Ehrenfried<sup>13</sup> as 5 to 2. There is no adequate explanation for this discrepancy which runs so true to form in different series. Trauma has been suggested as a factor.

Objective Findings.—The earliest manifestations are most frequently hard, irregular nodules on the skeleton in the region of the epiphysis of long bones. However, a parent may notice that the extremities of one side are shorter than those of the other (Ollier's type). Actual deformities of the bones may be observed, but as a rule these are not apparent as an initial manifestation. The abnormal bony prominences increase slowly in size, and others may appear. The areas of predilection are the juxtacpiphyseal regions, especially of the arms and legs. Clinical examination and knowledge may suggest it, but the roentgenogram later confirms the fact that these bony projections are on the diaphyseal side of the epiphyseal cartilage and that they are more inclined to be large and more numerous in the metaphyses, which have undergone the most rapid growth: thus, at the lower end of the femur, at the upper end of the tibia, lower end of radius and ulna, upper end of the humerus, lower end of the tibia and fibula, and the region of the elbow joints. The ribs are common sites, especially posteriorly near the tuberosities. Small exostoses occur frequently on the phalanges. The carpal bones are rarely the seat of exostoses, but they may be unequal in relative size34 (see also Case 1 in this paper). Relative unequality has been observed in the phalanges (Cases 1 and 3). The os innominatum is an infrequent location for exostoses, and the bones of the head and spine are less frequent locations. Osteochondromas do occur, even though rarely, on the skull and spine and even on

bones of the face (Ochsner and Rothstein<sup>35</sup>). The patient in Case 1 reported herein had an enlargement, evidently a chondroma, on the septal cartilage of the nose.

Shortness of stature is a common finding. In the Ollier type of dyschondroplasia the extremities of one side may be considerably shorter than those of the other. Hunter and Wiles<sup>17</sup> in 1935 collected twentynine unilateral cases with facial asymmetry in six. Ehrenfried<sup>13</sup> considers shortness of stature a common finding in the hereditary deforming dyschondroplasia type, and all the affected members of the family in Case 1 reported here were short—5 feet, 1 inch to 5 feet, 2 inches, while the unaffected members were invariably taller.

Certain deformities other than the bony prominences are likely to occur, and these are due to a relative deficiency in growth of some of the bones and irregularities in growth along an epiphyseal line. Some of these findings, while not constant, are quite characteristic, and while better appreciated in the roentgenograms they may be expressed clinically. A varus deformity may be present at the elbow (according to Keith<sup>12</sup> in one-third of the cases) and the head of the radius may be dislocated, the radius longer than the ulna, with ulnar deviation of the hand. The opposite relationship, i.e., ulna longer than radius, is far less common but does occur. Various abnormal curves may be present in the bones. A valgus deformity of the knees with knock knees is not uncommon, and valgus deformity of the ankle joints with the external malleolus much higher than the internal occurs. Pes valgus is not entirely explained on the basis of short fibula, as was suggested by Davis4 and Ehrenfried,25 but to a true deviation of the lower articular surface of the tibia (Fig. 12), which is occasioned by the unequal growth along the epiphyseal line, the inner part of the epiphysis growing faster than the outer end. Pes planus is a common finding because of the valgus deformity of ankle.

These individuals are of normal mentality and normal muscular development. They are not prone to become athletic like achondroplastic dwarfs and are not weak like the pitiful patients with Morquio's disease (Morquio,<sup>36</sup> Ruggles,<sup>37</sup> and Meyer and Brennemann<sup>38</sup>). They are not of an abnormally retiring disposition and are more amused by than ashamed of their malady, but are fearful of their offspring's being similarly affected. Calcium content of the blood is normal <sup>34</sup>

At maturity, the exostoses cease to grow, and deformities do not increase. The disease clinically remains stationary except in rare instances, in which exostoses may increase or decrease in size or rarer instances when they might appear for the first time (Honeij, 34 Davis 4).

Roentgenologic Characteristics.—There are certain features revealed in the x-ray films in the affections which the author, among others,

chooses to group under the heading "dyschondroplasia," which justifies the classification of all of them under the same name: The location of the affection, most marked in the metaphyses of long bones in which most rapid growth is occurring; second, the age period, youth and adolescence in which the abnormal findings are most marked. healing tends to occur by more uniformity of ossification. Third. irregularity and incompleteness of ossification near the epiphyses, indicated by clear areas, streaking, striation or stippling of the metaphyses. Fourth, long metaphyses, i.e., the broadness of the metaphyses extending for an abnormal distance on the diaphysis and not shading in the normal distance into the smaller diametered diaphyses. This indicates incomplete resorption (tubulation) or conversion of the metaphysis into the diaphysis, a process which I choose to name diaphysation. Fifth, exostoses, which may be a prominent clinical finding, but in the x-ray pictures their existence is shown to be not the fundamental process in the disease. Certain cases have but few small exostoses less striking than other roentgenologic characteristics that indicate a developmental defect of bone affecting mainly metaphyses which have undergone the fastest growth. In each type of dyschondroplasia there is a different degree of prominence of the various characteristic features of the disease.

In the hereditary deforming chondrodysplasia type practically all of these features are pronounced. The metaphyses are broad, and incomplete ossification results in diffuse osteoporotic areas. Irregular calcification results in appearance of longitudinal striation and stippled areas. Striped metaphyses are not so regular or so marked as in the Voorhoeve type, nor are the stippled areas so large or so pronounced as in the Albers-Schönberg type. Osteochondromas may be numerous and large. Both sides of the skeleton are affected, and clear, punched-out areas in the phalanges and metacarpals suggest enchondromas. Shortness of stature seems to be a constant finding.

In the Ollier type of dyschondroplasia the affection is usually unilateral with the affected extremities much shorter than the opposite side. Heredity is infrequently proved. There are longitudinal striations of the metaphysis and even stippling. Failure of diaphysation (process involved in transformation of the broad metaphysis into the narrow shaft) has been more gradual, less abrupt, than in the hereditary deforming chondrodysplasia type of dyschondroplasia. Asymmetry of the face may be found. Osteochondromas are less numerous, and on the whole, smaller. All features are found in both the Ollier type and the hereditary deforming chondrodysplasia type, but some characteristics are more pronounced in one type, some in another. It is not entirely a difference in intensity which distinguishes the two types. In Case 5 reported here, for example, the manifestations of dyschondroplasia are minimal, clinically latent, the

failure of diaphysation and small exostoses discovered by x-ray being the only features to distinguish it in the thirty-four-year-old patient.

In Voorhoeve's type the predominant finding is the peculiar insufficiency of calcification in the metaphyses with a pattern so regular that broad stripes caused by zones of deficient and more normal calcification result. The failure of diaphysation and exostoses are not so prominent as in the two preceding types.

In Albers-Schönberg's case<sup>28</sup> the small exostoses and slight tendency to retarded diaphysation are insignificant findings compared with the dense areas of increased calcification. This characteristic of involvement of the epiphyses, especially prominent in this type, is also found to a less extent in the Voorhoeve type and in the hereditary deforming chondrodysplasia type of dyschondroplasia in maturity. One of the most unexpected findings in Albers-Schonberg's<sup>28</sup> case is that the equality of stippling is as pronounced in the epiphyses as in the diaphyses.

The x-ray confirms many of the clinical impressions besides disclosing other characteristics of the disease. The head of the radius may be dislocated and the varus deformity of the elbow is seen to be due to relative shortness of the ulna, the distal epiphysis of which frequently shows various degrees of failure in development and growth. The radius is not invariably longer than the ulna. times the radius is shorter than the ulna, a condition I have seen, but this is extremely rare. The lower end of the ulna may be pointed with the portion of the bone just proximal to this broad, even broader than normal, incompletely ossified, and converging into the narrower, more normally ossified diaphysis. This particular deformity is called "arrowhead" and is characteristic of the disease. The radius and ulna may be widely separated due to exostoses. Synostoses may occur and frequently exostoses so prominent as to interfere with rotation of the forearm. A false joint more proximal than the distal radio-ulnar may form between the two bones. Ulnar deviation of the hand may result from the short ulna and ulna deviation of the distal articular surface of the radius.

Very characteristic changes also occur in the tibia and fibula. The knock knees frequently noticed clinically are found in the roentgenograms to be due to curves in the tibias and fibulas. These curves, most frequently concave outward, are at the upper and lower ends of the bones (Case 4) and are produced by irregular growth along the epiphyseal lines. The reason becomes more apparent when we view the roentgenograms in Case 1 (Figs. 2 and 4), and in certain instances the epiphyses are not normal in contour but are wavy in outline. The fibula may be shorter than normal, and the inferior articular surface of the tibia may be not at right angles to the longitudinal

axis of the shaft but may show marked outward deviation, throwing the foot into a valgus position with the outer superior margin of the astragalus pointing directly up between the tibia and fibula and some of the weight of the body being transmitted directly through the fibula on to the outer surface of the astragalus (Fig. 12). The shaft of the fibula then bearing weight shows the evidence of increased function by becoming thicker and more robust than normal. The tibia and fibula may fuse together at their upper and lower ends, and the two bones may be more widely separated than normal because apparently of exostoses pushing them apart.

Though the bones of the head and face and vertebral column are infrequently affected by the disease, they may show exostoses<sup>35</sup> and in Case 1 reported herein the skull showed irregular calcification characterized by a fine mottling. This appearance has not been previously described. According to Ehrenfried<sup>13, 25</sup> and Weinstein and Cotell,<sup>39</sup> the disease does not affect membranous bone. This assertion would not seem to be correct, but it is so that the membranous bones show little evidence of the disease and frequently show none. This is probably due to the fact that the disturbance is more marked where growth is occurring fastest.

Carpal and tarsal bones occasionally show evidence of the disease by irregularity in calcification<sup>29, 30, 34</sup> (and Cases 1 and 3 reported here). The relative sizes of the carpal bones may be disturbed<sup>34</sup> (and Cases 1 and 3). Inequality of the metacarpals is seen in the roent-genograms in Cases 1 and 3. This finding has already been recorded by Honeij.<sup>34</sup>

In the Ollier type of dyschondroplasia the phalanges frequently show clear areas which Ollier<sup>s</sup> has shown to be masses of cartilage cells (enchondromas). It is questionable, however, whether all clear areas in the bones are cartilage. This certainly has not been proved because biopsy specimens are very infrequent. The author believes because the subcortical areas of the osteochondromas do not contain cartilage (Fig. 5) that such clear areas as are shown in the upper end of the humerus in Case 4 are mainly filled with fat.

Osteochondromas affect mainly the juxtaepiphyseal region of long bones, and a peculiar finding is that the apex of these always points away from the nearest epiphysis. The author has studied x-ray films carefully to find an exception to this rule and to see if the exostoses are always directed toward muscle pull. On the head of the fibula, for example, the pull of the attached muscle is up and yet the exostoses point downward. No definite exception has been found to the rule and such uniformity of direction speaks in some measure for localized failure of diaphysation as at least an initial cause of the

exostoses (v.i.). The cortex of exostoses sometimes consists of cartilage, sometimes of bone. As maturity advances, ossification becomes more complete, and all osteochondromas tend to become exostoses.

Etiology, Pathogenesis, and Pathology,-Some observers have maintained that a relationship exists between multiple exostoses and rickets.1, 22 Ritter40 found a small thyroid in the affected members of an exostotic family. It is maintained by Dwyer9 and White41 that a definite relationship exists between achondroplasia and dyschondroplasia. Ehrenfried<sup>13, 25</sup> and others have firmly established a hereditary basis in a large percentage of the cases. In 236 cases collected by Ehrenfried,13 heredity was demonstrated in 176. It was not found in 18, and in the remaining 42 heredity was uncertain or not mentioned. In 3 of the 6 cases reported here a familial basis was established. Two of the remaining were clinically latent cases. Such cases may explain the difficulty of proving heredity in certain instances. In fact, so high is the percentage of cases with proved familial background that a negative history in a preceding generation not actually shown to be free of the disease by x-ray may be accepted with some doubt. Bentzon<sup>31</sup> attempted to prove experimentally that the sympathetic system was at fault. He hypothesized that there was vasodilatation. paper frequently quoted in the literature is far from convincing, and even he, after detailed experimental work in which he attempted to destroy the sympathetic system by cauterization and found no changes in the bones and in other experiments in which he attempted to destroy the vasoconstrictor nerves by injecting alcohol around the nutrient artery to the tibia with the result that transient osteoporosis occurred in I out of 6 cases, did not think that he had definitely proved his hypothesis. Richard, Dupuis, Roederer, and Froyez<sup>16</sup> do not believe Bentzon produced the disease. His roentgenograms and experiments are certainly not convincing.

Jansen<sup>26</sup> believes that the sympathetics are at fault but thinks it is a vasoconstriction rather than a vasodilatation. Freund<sup>32</sup> is of a similar opinion. The theory of sympathetic disturbance has insufficient evidence for its acceptance. The changes in the bone in dyschondroplasia are such that what we commonly find from even long-standing vasoconstriction or vasodilatation are not comparable. There is no evidence of soft tissue vascular disturbance and a contralateral case such as was reported by Molin is unexplained by such a theory. All of which would necessitate the assumption that there are multiple peripheral selected foci of action instead of a disturbance in the central sympathetic system, which necessary supposition makes the theory less acceptable. Bone grows in length at the diaphyseal side of the epiphyseal cartilage. Arthur Keith<sup>12</sup> states that John Hunter realized



not only longitudinal growth but also resorption of the broad metaphysis must occur to form the narrower diametered diaphysis. Keith elaborated this hypothesis in relation to dyschondroplasia which he chose to call "diaphyseal aclasia." He proposed the theory in explanation of dyschondroplasia that the epiphyseal plate grew faster than the periosteum covering it and that the cartilage was left without a limiting membrane, permitting the formation of exostoses. Furthermore, he presumed that tubulation or resorption of the broad metaphysis was delayed and that ossification was incomplete. Jansen<sup>26</sup> further elaborated this theory and reasonably explains the development of many of the features of dyschondroplasia. He states that no less than six, probably more, processes are involved in the development of bone and that any of these may be retarded or hastened. The processes he names are resorption, tubulation (diaphysation), cancellation, cell division, cell enlargement, and cell differentiation.

Jansen<sup>26</sup> thinks retardation of cell division accounts for irregularity (waviness) of the epiphyseal line. Local retardation of tubulation results in exostoses (Fig. 13) and complete retardation of cell division results in achondroplasia. His explanation is the most lucid description of the pathogenesis. But it doesn't explain all exostoses, certainly not those that project farther out from the shaft than the widest limits of the bone in its development. Only abnormal growth can explain such (Fig. 12).

In studying sections from the large osteochondroma removed from the femur in Case 1, the author was struck with the lack of any semblance of calcification of cartilaginous matrix. When bone grows at the epiphyseal line, the metaphyseal side of the cartilaginous plate made up of large cartilage cells and a cartilaginous matrix shows evidence of beginning calcification, forming the groundwork for the invasion of osteoblasts and the production of bone. In precartilaginous bone also in the embryo the earliest transition of the cartilaginous anlage into bone is the appearance of calcium in the matrix of deeper layers between the more mature cartilage cells. Then a process which is the result of osteoblasts and osteoclasts, using the calcified cartilaginous matrix to construct bony trabeculae, converts the preformed. partially calcified cartilage into true bone. Exactly what takes place at the epiphyseal line in these cases of dyschondroplasia, it has been the privilege of few to observe, but, if we presume that the cortex of the ostcochondroma is analogous to the true cortex of bone, we see a failure of a fundamental process in these cases, far earlier processes than diaphysation; i.e., a failure of calcification of cartilaginous matrix and a failure of osteoblasts to appear in adequate number and with sufficient activity from the marrow cavity and from the osteogenic layer of the periosteum. Except for lack of calcium precipitated in

these cartilaginous exostoses, probably every other factor is present for the formation of bone, in which instance the normal sequence may follow with no more insufficiently ossified areas, no exostoses. This failure of preliminary ossification of cartilage, however, does not alone

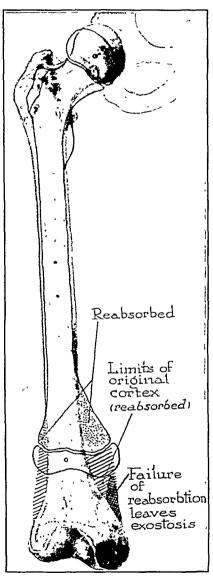


Fig. 13.—Diagrammatic representation of growth of femur. The two dots in the center of the bones do not change relationship with growth, but the circles in the epiphysis move away from the dots in the central portion. The dotted and shaded areas indicate the limits through which the bone develops in the adolescent to adult period. It is in this area of tapid growth that most changes occur in dyschondroplasia. Reabsorption normally results in diaphysis becoming more narrow than the metaphysis. Partial failure of this process (diaphysation) results in evostoses; complete failure results in broad metaphyses.

explain the whole process because it is certainly not called into question in the lack of longitudinal growth and the failure of development in certain cases of the terminal ends of the ulna.

The cause of the disease is obscure. Various theories have been announced: Thyroid deficiency, rickets, fetal rests,22 sympathetic imbalance, vasoconstriction and vasodilatation influence, 26, 32, 33 heredity,13, 25 and acquired transmissible characteristics from repeated fractures.3, 10 In considering the acceptability of these it is immediately apparent that the capriciousness with which the disease affects bones, its occasional unilaterality, or selection of even one extremity, is evidence against a cause or a deficiency circulating in the blood to reach in comparatively the same intensity all the extremities. The question of localization again, together with absence of other concomitant evidence to be expected and together with the incongruities of the disease picture with our present knowledge of the effects of hyperemia or ischemia on bone, is sufficient for withholding acceptance of theories of sympathetic imbalance. Our only reasonable explanation of the cause of the disease today is something in the cell, a deficient anlage. This is more tenable in those cases that are definitely proved familial. but is a less satisfying explanation for the sporadic case. Perhaps a localized deficiency, phosphatase shortage, or some analogous explanation will remove this condition from the category in which the etiology is unknown.

Prognosis for life is excellent. Few patients with the disease die because of it. At the end of adolescence, though as a rule no retrocession in the already developed deformities takes place, the condition becomes arrested. No new osteochondromas occur, no new deformities, and roentgenologically ossification apparently progresses toward the normal. Occasionally, though rarely, the pressure of an exostosis arising from the vertebral column results in pressure on the spinal cord. Aneurysms may develop from pressure of an exostosis, or nerve paralysis (see Chart 1 for relatives of patient in Case 1). Infrequent are such complications. More common is limitation of motion in joints; very common is interference with rotation of forearm. Fractures are infrequent.

Treatment.—Measures to stop the disease in the progressive stage are of no avail and are not found recorded. The theories of etiology other than heredity have not been sufficiently credited even by their sponsors, apparently, to have evoked a trial for correction of thyroid imbalance or sympathetic disturbance. Thymus extract has been administered in osteogenesis imperfects with beneficial effects on calcification.<sup>42</sup> Though not entirely analogous, it is possible that it may hasten ossification in this condition. Surgery must be frequently employed to remove osteochondromas which because of their size either

become prominently unsightly or interfere with function, osseous, nerve, or vascular. However, it is not necessary to employ it indiscriminately to remove the larger exostoses, as was done by one author.9 The dissection of the surrounding tissues should be extracapsular to insure against recurrence by leaving some of the cortical tissue behind. In dressing the wound a moist sea sponge or rubber bath sponge has the proper resiliency for compressing the tissues and avoiding dead space.

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# DIFFERENTIAL DIAGNOSIS OF POLIOMYELITIS

WITH REPORT OF A CASE OF DIFFUSE SARCOMATOSIS OF THE MENINGES SUSPECTED TO BE POLIOMYELITIS

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THE diagnosis of certain communicable diseases offers no particular difficulty to the practicing physician. For the past several years the initial diagnoses of patients sent to the Herman Kiefer Hospital with scarlet fever, erysipelas, measles, chickenpox, and whooping cough were substantiated in more than 90 per cent of cases. On the other hand, the diagnosis of a few communicable diseases is not so readily made. Patients sent to the hospital with an initial diagnosis of typhoid fever were verified as having this disease in only 51.9 per cent of cases during a five-year period. Poliomyelitis is also a disease the diagnosis of which may be attended with considerable difficulty. During the period 1927 to 1935, inclusive, 790 patients were admitted to the hospital with the diagnosis of poliomyelitis. Of these, the initial diagnosis was confirmed in 445, or 56.3 per cent.

The difficulty in differentiating poliomyelitis from general systemic or central nervous system infections is considerable because the diagnosis of the disease is at present not limited to frankly paralytic cases. A decade or two ago the diagnosis of poliomyelitis was made only when paralysis occurred. The diagnosis of nonparalytic poliomyelitis is now possible because of improved clinical and laboratory procedures. A careful study of familial contacts to known cases frequently substantiates the impression that so-called abortive cases do occur.

In the first or systemic phase, poliomyelitis differs in no important essential from the onset of the average acute general infection. It is not surprising, therefore, that in many instances patients apparently suffering from an infectious disease should be referred to the hospital with the diagnosis of poliomyelitis when this disease is prevalent. It is far better to err in this manner than to have omitted consideration of the disease, and physicians are to be commended for being alert to the possibility of poliomyelitis.

Table I gives the final diagnosis of cases referred to the Herman Kiefer Hospital as poliomyclitis for the period, 1927-1935, inclusive.

The table lists seventy-nine conditions encountered in patients referred to the hospital with the diagnosis of poliomyelitis. Upper respiratory infections accounted for the largest number of cases which by clinical and spinal fluid findings failed of verification. In 74 instances the

From the Divisions of Communicable Diseases and Pathology, the Herman Klefer Hospital.

TABLE I

FINAL DIAGNOSIS OF 790 CASES REFERRED TO THE HOSPITAL AS POLIOMYELITIS,
1927-1935

1021-1000					
	IBER	PER CENT	NUMB		PER CENT
DISEASE OF C.	ASES	OF TOTAL	DISEASE OF CAS	ES	OF TOTAL
Poliomyelitis 4	45	56.3	Abscess, inguinal 1		
Nasopharyngitis	74	9.4	Abscess, intraspinal 1		
	26	3,3	Alcoholic neuritis 1	-	
	19	2.4	Aortitis, chronic 1	-	
,	19	2.4	Asthma, bronchial 1	L	
, , , , , , , , , , , , , , , , , , , ,	18	2.3	Bronchitis, acute 1	Į	
licular	10	2.0	Bronchitis, chronic 1	l	
	17	2.2	Cardiovascular disease 1		
Meningitis, meningo- coccus	7 1	~	Cerebral thrombosis 1		
	16	2.0	Choren 1	l	
tillets business transfer	15 15	1.9	Colitis, mucous 1	l	
	$\frac{13}{12}$	* * *	Endocarditis, subacute 1	Ĺ	
	-	1.5	bacterial		
Pneumonia, bronchial	10	1.3	Erysipelas 1	l	
Encephalitis	8	1.0	Fracture, skull 1	ĺ	
Scarlet fever	6	0.8	Heart disease, congenital 1		
Serum sickness	2	0.6	Heat prostration 1	-	
Appendicitis	5	0.6	Hemangioma of meninges 1		-
Dysentery, bacillary	4	0.5	and brain	•	
Osteomyelitis	4	0.5	Hemorrhage, cerebral, 1	1	
Pyelitis	4	0.5	hemiplegia		
Meningitis, streptococcus	3		Hemorrhage, intracranial, 1	!	
Myelitis, transverse	3		of newborn		
Typhoid fever	3		Jaundice, acute, catar- 1	1	
Endocarditis, acute bac- terial	2		rhal		
Epiphysitis, acute	2		Lymphatic leucemia 1		
Exanthem subitum	2		Malnutrition 1		
Hysteria	2		Mastoiditis, chronic 1	Ļ	
Landry's paralysis,	2		suppurative		
nonpoliomyelitic			Measles 1		
Meningitis, Pfeisser	2		Meningitis, pneumococcie 1		
bacillus	_		Meningitis, type unde- 1	L	
Myositis	2		termined		
Nephritis, acute			Migraine 1		
No disease	2		Mumps 1		
Paraplegia, spastic, old	5		Paratyphoid fever B 1		
Peripheral neuritis—	2 2 2 2		Peritonitis, pheumococcus 1	Ĺ	
Bell's palsy	_		Rickets 1		
Poliomyelitis and whoop-	. 2		Sarcoma, spinal cord 1		
ing cough	_		Septic sore throat 1		
Sinusitis, acute	9		Septicemia 1		
Syphilis, congenital	õ		Status epilepticus 1		
Tuberculosis, acute,	2 2 2		Syphilis, cerebrospinal 1		
miliary	-		Tetanus 1		
Whooping cough	2		Traumatic injury of hip 1		
Abscess, cervical lymph	ī		Traumatic injury of knee 1	Į	
node	1		Vaccination, active 1		
Abscess, foot	1	-	Totals 790	)	99.7

diagnosis of nasopharyngitis was made. This condition may be a symptom of early poliomyelitis. Infections of the brain and spinal cord, taken as a group, were responsible for 73 cases. Pneumonia accounted for 22 cases. Acute rheumatic fever occurred 19 times in this series. The remainder of the list includes conditions which occurred with less frequency and shows a wide range of possibilities of error in making a diagnosis of poliomyelitis.

The diagnosis of conditions listed in the table was made clinically, aided by laboratory findings. At the present time animal protection tests are not feasible as a routine procedure for verification of the diagnosis of poliomyelitis in suspected cases. Latitude in the inclusion of so-called abortive and nonparalytic cases of poliomyelitis, which might have been eliminated as the result of animal tests, is probably offset by the exclusion of cases with upper respiratory infections in which no history of contact with a known case is given, but which might have been verified as poliomyelitis by animal tests.

In general, certain clinical findings discount the importance of the consideration of poliomyelitis as the diagnosis in a suspected case. Briefly, they are as follows:

- 1. Irrationality or Coma.—These states are uncommon in poliomyelitis, but one or the other is frequently seen in meningitis of all types, cerebral accidents, cerebral manifestations of acute nephritis, or diabetes.
- 2. Marked temperature elevation, with pronounced fluctuations of the septic type. Temperature is generally moderately elevated in poliomyelitis. Septic temperatures suggest pyelitis, otitis media, typhoid fever, undulant fever, tularemia, malaria, or sepsis.
- 3. Convulsions.—This phenomenon may occur in poliomyelitis but usually accompanies the acute onset of a severe infection in infants and small children. Consideration must be given to tetanus, pneumonia, tetany, status epilepticus, an acid-base imbalance, or an acute gastro-intestinal disturbance.
- 4. Meningismus.—This condition is generally a temporary meningeal irritation which may occur during the course of acute infectious diseases. Symptoms are, as a rule, less severe than those of a purulent meningitis, and characteristically there is a rapid recession of symptoms following relief of pressure by lumbar puncture. The spinal fluid cell count is low, and no organisms are present.
- 5. Severe Pain or Swelling of Affected Extremities.—Hyperesthesia is common in the early central nervous system phase of poliomyelitis, but pain is unusual. Swelling of an affected part is not caused by this infection. The presence of one or both of the conditions should call to mind ostcomyelitis, epiphysitis, bursitis, suppurative arthritis, acute rheumatic fever, myositis, or abscess of soft parts.
- 6. Cervical Lymphadenitis.—When noticeable and painful enlargement of the cervical lymph nodes is present, the diagnosis is likely to be one of the following infections: diphtheria, scarlet fever, septic sore throat, infectious mononucleosis, peritonsillar or retropharyngeal abscess, tonsillitis, tuberculous lymphadenitis, leucemia, or serum sickness.
- 7. Abdominal Tenderness.—This sign may be elicited during the systemic phase of poliomyclitis and is generally attributed to the effect of the virus on the mesenteric lymph nodes, Peyer's patches, and the spleen.

Generalized abdominal tenderness is a common accompaniment of typhoid and paratyphoid fever, dysentery, colitis, or peritonitis. Localized tenderness should direct attention to the appendix, gallbladder, kidney, or uterine adnexae and occasionally to a diaphragmatic pleurisy or beginning lobar pneumonia

8 A Prolonged Illness With Subsequent Paralysis — Weakness or paralysis usually develops within a week of the onset of poliomyelitis. The late occurrence of paralysis is commonly seen in diphtheria.

In spite of careful attempts to avoid pitfalls in the diagnosis of poliomyelitis, an occasional bizarre condition presents itself which is provocative of a diagnosis wide of the mark. Even unusual cases offer clues which, if recognized, would lead to a more accurate diagnosis. Such a case was seen on the service of this hospital during the month of July, when cases of poliomyelitis normally begin to be reported. The history of onset, the findings upon physical examination, and the subsequent clinical course of the illness drew our attention sharply to the consideration of poliomyelitis as the diagnosis in this instance. The history and the clinical course of the case were as follows:

The patient was an eleven year old white male, who was admitted to Herman Kiefer Hospital on July 17, 1935, with a diagnosis of suspicious poliomyelitis. The boy gave a history of having had scarlet fever several years ago. He was suc cessfully vaccinated against smallpox and diphtheria in 1933. There was no his tory of tuberculosis in the family. About June 28 the patient jumped from a porch and fell. He did not complain at the time of the fall. On or about July 3 he be gan to complain of pain in the back and stomach. This complaint was presented at intervals for a week following this date and more frequently at night. The pain was evidently not severe enough to prohibit the patient from going in swimming several times during the interval. On July S the patient began to limp on the right foot, and to complain of pain in the right heel. He was taken to a physician a few days later because of increasing and gradual inability to walk. Complete inability to walk occurred on July 15. On July 16 the patient complained of pain in the neck and his physician did a lumbar puncture, in the home, and removed 5 e.c. of ap parently anthochromatic fluid, said to have been under some increase of pressure The boy was admitted to Herman Kiefer Hospital on the following day with a diagnosis of suspicious poliomyelitis

Physical Examination—The patient was well developed and well nourished and appeared acutely ill. The skin was negative except for a contusion present on the left leg below the knee. Examination of the eyes, ears, and nose gave negative results. A slight injection of the nasopharyngeal structures was noted. The heart and lungs were negative to percussion and auscultation. The abdomen was tense on palpation in the lower quadrants; dullness to percussion was present above the symphysis public. The left testicle was not completely descended. There was flaccid paralysis of the lower extremities and complete anesthesia of the lower half of the body to within 3 inches of the nipple line. Priapism was marked and persistent. Micturition was involuntary and bladder function appeared to be automatic. The biceps and triceps refleves were hyperactive. The umbilical and cremasteric refleves and the knee and ankle jerks were absent. The Babinski and Brudzinski signs were negative. The patient had a stiff neck and back.

The temperature, on admission, was 100° F., the pulse rate 110, the respiratory rate 22. The blood count taken on the day of admission showed: red blood cells, 4,530,000; hemoglobin, 80 per cent; white blood cells, 17,500, of which 93 per cent were polymorphonuclear leucocytes and 7 per cent small lymphocytes.

Lumbar puncture was attempted by three members of the staff, but spinal fluid was not obtained. A cisternal puncture was successful and 15 c.c. of clear fluid were removed. Examination of the spinal fluid showed a cell count of 290; globulin, negative; differential count, 50 per cent lymphocytes; Gram stain, no organisms; quantitative sugar determination, 107 mg. per 100 ml. The spinal fluid Kahn was negative.

Roentgenologic examination of the spine revealed no evidence of bone injury or bone disease.

Subsequent Course.—There was no evidence of involvement of upper cord or higher brain centers throughout the first hospital day. Examination on the morning after admission showed a loss of sensation up to the nipple line and loss of all movement of both lower and upper extremities. During the morning the patient appeared rather drowsy although he responded to stimulation. A lumbar puncture was attempted and again proved unsuccessful. At a subsequent cisternal puncture 15 c.c. of clear fluid were removed under slight increase of pressure. The cell count was 25; globulin, one-plus; Gram stain, no organisms; quantitative sugar determination, 75 mg. per 100 ml.

About 10:30 a.m. the patient complained of being hungry. At dinner time (11:30 a.m.) he ate well and experienced no difficulty in swallowing. At 12:45 p.m. the patient complained of difficulty in breathing, but cyanosis was not present. During the remainder of the afternoon there were spells of restlessness followed by intervals of drowsiness. On examination at 4:30 p.m. respiratory movements were retarded. Diaphragmatic function did not appear to be impaired, but paralysis of the intercostals was evident. The patient's color became slightly cyanotic, and artificial respiration was resorted to until the patient could be placed in the Drinker respirator. Therapeutic stimulation and hyperventilation in the respirator were of no avail, and the patient died, approximately eighteen hours after admission to the hospital.

#### COMMENT

The history and general course of illness in this case were not materially different from those seen in a Landry's type of paralysis in polio-There are a few findings which may appear difficult to harmonize with a diagnosis of poliomyelitis: notably, (1) the history of a fall. Not infrequently this may be incidental to or possibly serve as the contributing cause of a poliomyelitic infection. (2) The finding of xanthochromatic fluid. On an initial lumbar puncture one may encounter bloody fluid due to trauma at the time of the puncture, and this may occur in a frank case of poliomyelitis. However, xanthochromatic fluid should not be present in this disease on an initial lumbar tap. Subsequent lumbar punctures were unsuccessful, but two cisternal punctures showed a colorless fluid. (3) Sensory paralysis. paralysis is possible without motor paralysis and does occur along with motor paralysis in poliomyelitis. The virus may affect not only anterior horn cells, but adjacent nerve cells as well. Edema and congestion may he so pronounced that the spinal cord is unusually firm. Under such circumstances there may be loss of both motor and sensory function.

The history of a fall and the report of xanthochromatic fluid suggested a traumatic myelitis with hemorrhage. Subsequent rapid progression of paralysis seemed to warrant less consideration of this possibility.

With the exception of the appearance of xanthochromatic spinal fluid, the findings mentioned above did not appear to give sufficient weight to seriously call into question the credence of a diagnosis of poliomyelitis, and the patient came to autopsy with this clinical diagnosis. One member of the clinical staff disagreed with the diagnosis of poliomyelitis, although entertaining no definite idea with respect to the pathologic picture.

Autopsy.—The autopsy was performed three hours after death. There was marked flaccidity of the muscles, and the body was still warm. A yellowish green contusion, about 3 cm. in diameter and very slightly elevated, was noted on the anterior lateral surface of the left leg about 15 cm. below the knee.

The heart was of proportionately normal size. The right auricle and ventricle were relaxed but not dilated. The left auricle and ventricle were well contracted. The lungs were normally air containing throughout. The bladder contained about 250 c.c. of clear urine. The subarachnoid spaces contained slightly more than the normal amount of clear fluid. The bony and ligamentous walls of the spinal canal showed no evidence of preexisting injury.

When the spinal dura was exposed, it was seen to be markedly distended, having a maximum lateral diameter of about 16 mm, at the level of the ninth thoracic vertebra, where it appeared to be filled by the greatly swollen spinal cord. Visible through it were dull red and bluish green discolorations of the cord. The swelling extended from the level of the fourth thoracic vertebra to the level of the second lumbar vertebra. At the level of the twelfth thoracic vertebra, the dura was less tense, and there was a dark bluish red discoloration with the appearance of intra dural hemorrhage.

Removal of the cord and reflection of the dura revealed the leptomeninges of the lower portion of the lumbar swelling filled with dull red blood completely encircling the cord (Fig. 1). The upper level was fairly well demaicated on the posterior aspect and was more distinct and about half a segment lower on the anterior aspect. The hemorrhage decreased in amount among the nerve trunks of the upper portion of the cauda equina.

About the area of hemorrhage, the normally narrow thoracic portion of the cord was swollen to a maximum lateral diameter of 16 mm, and mottled with bluish green and dull red discolorations of maximum intensity on the posterior surface. On the anterior surface, the blood vessels were engaged. The swelling and discoloration gradually decreased in the upper thoracic portion and disappeared in the cervical swelling.

The picture presented was that of a transverse hemorrhage and the cord changes seen above the hemorrhage were interpreted as ascending degeneration. The finding of hemorrhage substantiated the attending physician's report of anthochromatic fluid and the swelling of the cord was sufficient to account for the failure to obtain spinal fluid at subsequent lumbar punctures.

In the absence of any injury to the spinal canal, the hemorrhage and degeneration were thought to be of an inflammatory origin and, while recognized as atypical for poliomyelitis, no explanation which rationalized all the findings was offered.

Microscopic examination of sections revealed the true nature of the condition. What had appeared as the swollen spiral cord was a diffuse neoplasm distending the

leptomeningeal spaces and distorting and invading the cord. In the zone of hemorrhage (Fig. 2) are numerous large, thin-walled spaces lined with endothelium and filled with blood which, at low magnification, have the appearance of an angioma.

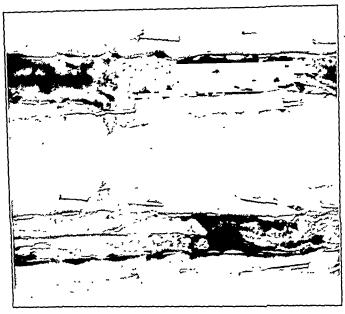


Fig. 1.—Anterior and posterior surfaces of the spinal cord showing hemorrhage in the region of the lumbar enlargement and marked swelling and discoloration of the thoracic cord.



Fig. 2.—Section from the deeply discolored lumbar region showing large anglomatous blood spaces surrounded by tumor cells with hemorrhage.

A few of these spaces contain unorganized thrombi. Around the spaces and the nerve trunks is a loose mat of spindle cells in intimate relation with the adventitia of the blood vessels (Fig. 3). A few round and polyhedral cells are also present, and there are extravasated red blood cells scattered throughout the tissues.

Sections from the region of maximum swelling (Fig. 4) show the tumor mass occupying more than two-thirds of the area of the cross-section of the cylinder with the remnants of the cord in the anterior portion. There was a wedge-shaped mass

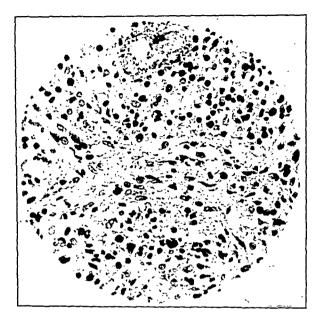


Fig. 3.—Cell character of the tumor in the lumbar cord.



Fig. 4.—Section from the thoracic cord showing that what appears as the swollen spinal cord in Fig. 1 is tumor. The distorted and invaded cord surrounded by tumor can be seen in the anterior portion of the section.

of tumor spreading the posterior median portion of the cord and extensive invasion of the cord tissue by tumor cells. In this region (Fig. 5) the tumor contains many

engorged small blood vessels, and the tumor cells are less differentiated than those around the large blood spaces, and round nuclei are more numerous. In many areas, the nuclei were grouped, suggesting a pseudoalveolar pattern, and large cells are fairly numerous. There were extensive areas of early degenerative changes.

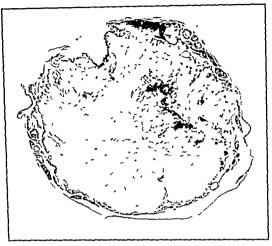


Fig. 5.—Section showing pleaus of small blood vessels, a developmental stage intermediate between Figs. 2 and 4.

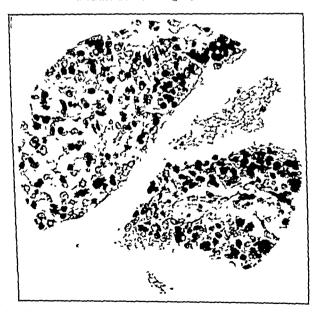


Fig. 6 -Cell character of the tumor in and above the upper thoracic cord.

At higher levels of the cord, its invasion and distortion became less, and the layers of tumor cells on the pia became thinner. Groups of tumor cells were found along the leptomeningeal blood vessels and pia of the medulla, eisterna pontis, and eisterna interpeduncularis and, also, along the attachments of the choroid plexuses of the fourth, third, and lateral ventricles, and a small mass of tumor cells was found in the infundibular recess.

Above the thoracic cord, the tumor consisted of fairly uniform cells with large, slightly oval nuclei having reticulated chromatin, the relatively scanty cytoplasm forming a delicate meshwork (Fig. 6).

An excellent description of this type of tumor is given by Ewing, under the heading, "Diffuse Sarcomatosis of the Meninges." This tumor seems particularly to justify Ewing's statement that the recognition of a specific form of diffuse angioblastic meningeal sarcoma seems warranted.

#### DISCUSSION

The finding of xanthochromatic fluid was an important clue to the final diagnosis. The slight consideration this clue was accorded resulted less from lack of appreciation of its importance than from doubt concerning the reliability of its report.

The fall sustained by the boy may have accounted for some or all of the hemorrhage of the cord, but it would seem just as likely that the boy fell because some weakness of the lower extremities was already present. The latter explanation would appear to be more in keeping with the delay which ensued between the fall and the patient's first complaint. Again, progression of paralysis was not so rapid that swimming was impossible several times during the two-week interval between the fall and the seeking of medical aid.

When the extent of the pathologic process is considered, it is amazing that the patient remained apparently symptom-free for so long a period of time. The patient began to limp eleven days before he died, and progression of paralysis did not appear rapid until difficulty in walking occurred. The interval between complete inability to walk and death was three days.

#### SUMMARY

The differential diagnosis of poliomyelitis is presented, and a case of diffuse sarcomatosis of the spinal leptomeninges is reported, with a discussion of the diagnostic difficulties encountered.

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## ADRENAL NEUROBLASTOMA IN CHILDREN

### WITH REPORT OF TWO CASES

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THAS been known for many years that tumors arise from the I medulla of the adrenal gland. In the older literature these were called neurocytomas. Virchow9 in 1864 recognized that such tumors were associated with the sympathetic nervous system, from which the adrenal medulla is developed and called these tumors gliomas. chand in 1880 described a case of tumor of the adrenal medulla which occurred in a child nine months of age and interpreted it as a reproduction of the anlage of the sympathetic nervous system. Pepper<sup>c</sup> in 1901 described a group of cases which he collected from the literature and from his records, in each of which the primary tumor was in the right adrenal. He called these "congenital sarcomas." All of these cases presented similar clinical and pathologic pictures; they occurred in infants; they were very malignant, metastasizing early to the liver but never to the skull or long bones. This group of cases, with others which have occurred since, have been known as the "Pepper type of neuroblastoma."

Hutchinson<sup>2</sup> in 1907 described thirteen cases of primary tumor of the adrenal which he observed or selected from the literature, in which the primary tumor was in the left adrenal medulla. These cases had widespread tumor metastasis in the retroperitoneal lymph glands, skull, and long bones, but no metastasis in the liver. They also showed proptosis and increased intracranial pressure.

Wright<sup>11</sup> in 1910 was one of the first to give a complete histologic description of these tumors and classify them according to their origin. He demonstrated nerve fibers and rosettes, such as are seen in the anlage of the sympathetic nervous system from which the adrenal medulla is developed. He called these tumors neuroblastomas.

Robertson<sup>7</sup> in 1915 correlated the terms used by various writers in classifying tumors of the adrenal medulla. He suggested a classification based on the structural differences, such as sympathoblastoma, ganglioneuroblastoma, ganglioparaganglioneuroblastoma, ganglioglioneuroblastoma.

Scott, Oliver, and Olivers in 1933 made an extensive survey of the literature on tumors of the adrenal medulla. They found 158 eases in the literature and added four of their own. They have accepted the classification of Bailey and Cushing, 12 who in their monograph

"Tumors of the Glioma Group," use the term "sympathoblast" for the primitive pluriopotential cell before it has taken on the characteristics of a unipolar neuroblast. The sympathoblast corresponds to their medulloblast of the central nervous system. The classification they use is based on the dominant cell type:

- 1. Completely undifferentiated sympathicoblastoma.
  - a. Sympathogonioma with migratory cells and very malignant.
  - b. Sympathoglioblastoma, more mature with true rosette formation.
  - c. Sympathoblastoma. No such tumor was found in their series.
- 2. Incompletely differentiated tumors.
  - a. Sympathetic neuroblastoma. These may have nerve fibers and are usually less malignant.
  - b. Spongioblastoma.
  - c. Chromaffinoblastoma. An early form of the chromaffin reaction cell of the sympathetic nervous system of the medulla.
- 3. Completely differentiated tumors.
  - a. Ganglioneuroma. Mature ganglion cells and nerve fibers.
  - b. Chromaffinoma similar to chromaffin cells of adrenal medulla.

By this classification 83 of the 162 cases were sympathoblastomas, or completely undifferentiated tumors; 15 were sympathetic neuroblastomas, or partially differentiated tumors; 8 were ganglioneuromas; and 56 could not be classified because of inadequate records.

The age incidence varied with the type of tumor found. The undifferentiated tumors occur chiefly in infancy and early childhood. The majority of the partially differentiated tumors occur late in childhood and a few during early adult life.

The degree of malignancy is inversely proportional to the degree of differentiation of the tumor cells. The undifferentiated type shows early widespread metastasis and is almost uniformly fatal. Lehman<sup>3</sup> reports a patient living fifteen years after removal of an adrenal tumor, which was proved to be neurocytoma by histologic examination. This is the exception since most of the patients present themselves to the physician after metastasis has occurred when surgical measures are hopeless.

The first case we are presenting would be classified as a Hutchinson's type of completely undifferentiated sympathicoblastoma of Bailey and Cushing.<sup>12</sup> or neuroblastoma of Robertson.<sup>7</sup> This case differs from any in the series of 162 reported in that it is a Hutchinson type of tumor, with primary bilateral adrenal tumor.

#### CASE REPORT

CASE 1.—The patient, a five-year-old female, was admitted to Dr. Alton Goldbloom's service at Children's Memorial Hospital, Montreal. She had no illnesses with the exception of measles at the age of three.

In July, 1932, she developed high fever with vomiting, and severe pain in the left knee without redness or tenderness. The pain gradually decreased, to recur again in three weeks. In September, two months after the onset of symptoms, the parents noticed prominence of both eyes but especially the right. On Nov. 15, 1932, she was admitted to the Children's Memorial Hospital with complaints of an enlarged head, painful left leg, prominence of her eyes, and hemorrhage of the eyelids.

Family History.—Her father, mother, and three sisters are alive and well. There are no children dead. There was nothing of importance in the family history.

Physical Examination.—Examination of the child on admission showed an alert child, of normal mentality, with a large head, dilated scalp veins, bilateral proptosis, which was more marked on the right, hemorrhage into the right eyelid, all suture lines open and separated with soft tissue bulging through, and marked enlargement



Fig. 1.-Photograph of child at time of admission.

of the cervical and inguinal lymph glands. The chest was of the thin type. Breath sounds were normal. A soft systolic murmur was heard over the apex of the heart and over the nortic areas. The abdomen was protuberant and slightly tender in the upper half with no localization of the tenderness. The liver was palpable, three fingerbreadths below the costal margin in the midelavicular line.

In the midline of the abdomen was a hard, rounded, fixed mass which was only slightly tender. The mass was the size of a small orange and fixed to the deeper structures.

Neurologic examination was negative.

The eyes showed bilateral exophthalmos with limited occular movements, dilated veins of the cyclids and a distinct pallor of the optic disks.

The above symptoms and signs progressed until the right eye became almost enucleated before death. The abdominal tumor enlarged and a low grade fever persisted. Death occurred on Jan. 17, 1933, six months after the onset of her first symptoms.

Laboratory Findings.—Blood: red blood count, 1,310,000; white blood count, 6,200; hemoglobin, 45 per cent (Sahli); differential blood count showed polymorphonuclear leucocytes, 24 per cent neutrophiles, 3 per cent eosinophiles, 0 per cent basophiles, 1 per cent myelocytes. 1 per cent monocytes, and 71 per cent lymphocytes. The blood Wassermann test was negative.

The spinal fluid was clear and under increased pressure. The Pandy test was positive with no increase in cells. The total protein was 0.033 per cent and the sugar level, 0.09 per cent.

The urine was normal, and Bence Jones bodies were absent.

The roentgenologic report on November 15 was as follows: "There is evidence of widespread newgrowth involving the bones of the skull, humeri, right scapula, pelvis, and both femori. There is separation of the sutures of the skull."

Summary of the Autopsy Report.—The autopsy, performed sixteen hours after death, revealed a very poorly nourished white female child.



Fig. 2.—Photograph of liver, stomach, and first portion of small bowel with the large retroperitoneal tumor.

The peritoneal surface was smooth and glistening. A large tumor mass was present in the upper abdomen pushing the stomach and colon forward (Fig. 2). The mass was hard, nodular, purple in color, retroperitoneal, and filled a large portion of the abdomen measuring 13 by 13 by 15 cm. Two smaller tumors, each measuring 5 cm. in diameter, were attached to the iliac bones.

The liver was small, reaching just to the costal margin and showed no metastasis on its surface or on cut section. The cut section was brown with a fine yellow mottling.

The kidneys and adrenals were in relatively normal position. Both kidneys were normal in size. The right adrenal gland was replaced by tumor tissue which measures 2 by 3 cm. in diameter. On cut section the kidneys appeared normal. The tumor tissue of each adrenal was bluish purple in color, very soft, showing some necrosis near the center. The adrenal tumors were not part of the large retroperitoneal tumor mass (Fig. 3).

The lungs, heart, thyroid, thymus, spleen, stomach, pancreas, and intestines were normal with no sign of tumor metastasis.

The glands of the mesentery were large and hard, measuring from 1 to 2 cm. in diameter and were replaced by tumor tissue. All cervical, mediastinal, retroperitoneal, and inguinal lymph glands were enlarged, measuring from 1 to 4 cm. in length, were dark blue in color, very firm, and were replaced by tumor. Cut section of these appeared purple in color, the tissue very friable.

The periosteum over all the ribs was thickened. There were numerous purplish areas of discoloration beneath the periosteum which were found to be tumor tissue replacing bone. The anterior surface of the bodies of the vertebrae presented a picture similar to that described in the ribs.

The head was very large showing numerous large dilated scalp veins. The sutures were separated from 1 to 2 cm. with soft tissue bulging through the openings. When the scalp was reflected, the periosteum of the skull presented numer-

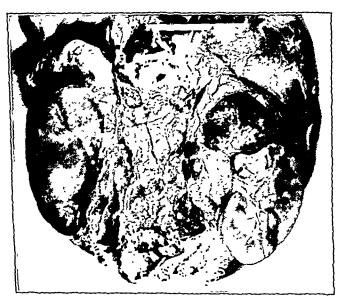


Fig. 3.—The section shows normal liver and kidneys with the large tumor replacing the right suprarenal gland and the multiple retroperitoneal metastasis

ous bluish discolorations which were slightly raised and soft (Fig. 4). The skull-cap was removed by cutting along the suture lines. The inner table of the skull was completely replaced by tumor tissue, which was soft, reddish in color, and very easily broken apart. In places the skull was of paper thinness. The tumor tissue surrounded the entire brain, being firmly adherent to the dura and making a pad from 1 to 2 cm. in thickness. Tumor tissue invaded the lateral, transverse, and longitudinal sinuses, almost completely occluding their lumina. A few of the large veins over the vertex of the brain were thrombosed by tumor tissue. The bone forming the wall of the orbit and the orbit itself were invaded by tumor tissue. The intraorbital pressure pushed the eye forward. There was no actual tumor involvement of the globe. There was marked conjunctivitis. A pad of tumor tissue covered the floor of the cranial cavity replacing part of the bony structure.

The lower half of the right femur was exposed, and a cylindrical soft tissue mass was found surrounding the lower 11% inches of the femur, which had the appearance of the tumor tissue previously described.

The entire picture was that of a neoplasm arising as a bilateral adrenal tumor with metastasis in all of the bones and lymph glands, with the liver and lungs escaping.

The following microscopic description is based upon sections made from the primary tumors of the adrenals and their metastasis. Both the sections of the tumors and the metastasis are similar.

"Sections through the tumor of the adrenal show an encapsulated tumor with a small area of adrenal cortex. The cells here are normal. These are surrounded on all sides by tumor cells which infiltrate this area. The tumor consists of a rich cellular material irregularly distributed through which are areas of hemorrhage and necrosis. Irregularly distributed bands of connective tissue are present within the tumor substance. In these bands are numerous thin-walled blood vessels. By far the greatest amount of the newgrowth is made up of specific tumor cells. These cells vary in size, shape, staining reaction, and arrangement. The majority are small, round; they stain deeply and show either no demonstrable cytoplasm or only



Fig. 4.—Photograph of the skull after removal of the scalp showing the multiple metastasis of tumor.

a rim of such. There are a good many large cells several times the size of those described. Some of the large ones are multinucleated. As a rule, the tumor cells are irregularly distributed. In some places, however, they arrange themselves around a common lumen, resulting in a glandlike structure, the so-called rosette formation. In most instances the hemorrhage occurs in the region of the central area of irregularly outlined masses of tumor cells. The necrotic areas vary a good deal; some show necrosis of long standing with deposition of lime salts. There is no evidence of acute inflammation. In one area there is a blood vessel just below the surface with tumor cells in the lumen. These tumor cells are similar to those in the main tumor mass.

"The metastatic lesions are similar to the primary tumor described above. Besides the tumor cells within the blood vessels of the capsule of the adrenal tumor, cells are seen in the vessels elsewhere. Those around the aorta show a very marked change. Hemorrhage in some of the metastatic lesions is more marked than in the original tumor. No nerve fibers have been demonstrated."

Microscopic Diagnosis: Neuroblastoma.

Case 2.—The patient was a three-year-old white female who was first seen on October 15. The parents said that the child had been complaining of abdominal pain for about two months. The pain had been intermittent, appearing for about one hour and then disappearing for a day or two. It was not associated with meals, and often it came on at night while she was in bed. The pain was never very severe, and it could not be well localized. About one week before admission to hospital the pain was a little worse, and with it there was some anorexia, constipation, and fever of one to two degrees Fahrenheit. Examination on admission revealed a fairly well-developed and well-nourished girl who at the time did not appear to be suffering pain. There was moderate resistance in the upper right quadrant of the abdomen, and a mass, which was considered to be kidney, could be palpated. The temperature was 99° F.; the leucocyte count was normal. During a week's observation in the hospital the child had no pain; her appetite was fair; and there was no abdominal tenderness. She was discharged to her home with instructions to return to hospital if the symptoms recurred.

About a week after discharge the child had a recurrence of her former symptoms. She was readmitted to hospital where a barium series was done and nothing abnormal was found. The child began having a low grade fever of 99 to 101° F.; the liver was slowly enlarging, and the child was becoming anemic. The blood examination showed 4,100,000 red blood cells, 66 per cent hemoglobin, 361,000 platelets, 0.5 per cent reticulocytes, coagulation time, 9 minutes (Lee and White); differential—69 per cent polymorphonuclears, 20 per cent lymphocytes, 7 per cent monocytes, and 4 per cent basket cells. The blood Wassermann test was negative. Cystoscopic examination revealed a normal bladder with normal urine coming from both ureters. Pyelograms showed the right kidney displaced downward and slightly outward but otherwise normal. This displacement was considered to be due to the enlargement of the liver. The urine cultures were negative, agglutinations of the blood for typhoid-paratyphoid group of organisms were negative, and examination of the stool for intestinal parasites was negative. Roentgenograms of the chest were negative.

The child continued to have slight fever, the liver enlarged, there was some slight resistance in the right upper abdomen with no tenderness, and no masses were felt at this time. The anemia became more marked, and the child became apathetic.

An exploratory laparotomy was performed by Dr. Dudley Ross, who reported: "A paramedian incision, extending from 1 inch below the xiphoid to slightly below the umbilicus on the right, exposed a large liver, which appeared to be pushed down and forward. There was no free fluid in the abdomen and no evidence of tumor in the liver. In the midline at the root of the mesentery of the small bowel could be felt a large mass of enlarged glands, rather firm and extending up into the upper right abdomen where they were connected to a large retroperitoneal mass located in the region of the adrenal gland. One of the lymph glands was removed for histologic examination. There were no further tumor masses felt in other parts of the abdomen."

The following microscopic description is made from a section prepared from a lymph node removed surgically from adjacent to the large tumor. The sections show a very hemorrhagic newgrowth. The cells of the newgrowth vary in size, shape, staining reaction, and arrangement. Most of them are very small and stain very deeply with hematoxylin and have little or no cytoplasm. This type makes up most of the tumor. There are some cells of the general type described, yet they are quite large. There is very little evidence of necrosis in the tumor. There are some quite well-defined rosette formations. No nerve fibers have been demonstrated.

Histologic Diagnosis.—Metastasis of neuroblastoma primary in the adrenal.

After the diagnosis had been made, the parents decided to remove the child to
their own home. At the time of discharge, five months after the onset of first

symptoms, the child was very anemic; she had marked anorexia; and liver and abdomen were very large. Roentgenograms were taken of the chest, skull, and long bones just before discharge from the hospital, and there was no evidence of metastasis in any of the regions examined. She died at home April 8, 1934, eight months after the onset of her first symptoms. Postmortem examination was not made.

The diagnosis of neuroblastoma was made by biopsy. The findings of a right-sided tumor in the region of the adrenal gland and a large liver at operation and the lack of x-ray evidence of bony involvement would point toward a Pepper type of neuroblastoma.

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# ACUTE "PRIMARY" STREPTOCOCCUS PERITONITIS

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THE mortality in "primary" peritonitis is so exceedingly high that it is a disease which warrants serious consideration, even though the condition is rare. During a period of one month in the winter of 1935, there were admitted to the Abraham Jacobi Division for Children of the Lenox Hill Hospital four cases of peritonitis, which did not follow the perforation of an abdominal viscus. Such cases are usually classed as primary, although all followed a respiratory infection, and all had abnormal findings in the fauces or the lungs. It is difficult to give a satisfactory definition of primary peritonitis. The simplest is that of Duncan, who says, "The term 'primary' is reserved for those cases which suddenly develop peritonitis unassociated with evidence of a preexisting abdominal inflammation." Thus cases of peritonitis following appendicitis, suppuration of mesenteric or retroperitoneal lymph nodes, osteomyelitis of the hip with extension into the abdominal cavity, or peritoneal injections are excluded from this category. Limited by this concept, we are including summaries of nine cases of primary streptococcus peritonitis which have been admitted to the Willard Parker Hospital during the past ten years and which have not previously been reported.

Etiology and Incidence.—The bacteria causing primary peritonitis are usually streptococci or pneumococci, although occasional cases are due to staphylococci and even more rarely to other organisms. The incidence of primary peritonitis, as given by different authors, varies from 1 to 10 per cent of all abdominal surgical emergencies in children. The average incidence in large pediatric surgical services is about 3 to 5 per cent of acute abdominal conditions, although it must be realized that many cases do not come to the operating table. Including the twelve streptococcus cases reported in this paper, we have collected records of 308 proved cases of primary streptococcus peritonitis. Cases due to the pneumococcus are somewhat more common, and those due to other bacteria are much more rare.

Portal of Entry.—The organisms enter the body through either the nasopharynx, the gastrointestinal tract, or the female genital tract. In many cases of pneumococcus peritonitis, the pneumococci undoubtedly enter by the last named route and reach the peritoneum through the fallopian tubes.¹ But there are many pneumococcal cases in which one

From the Abraham Jacobi Division for Children of the Lenox Hill Hospital, service of Dr. Jerome S. Leopold, and the Willard Parker Hospital, Department of Hospitals,

of the other routes is obviously alone implicated. In practically all instances of streptococcal peritonitis the streptococci first lodge in the nasopharynx.

Preceding Infections.—In all series of reports of streptococcus peritonitis, a large proportion of the cases had an upper respiratory infection or pneumonia immediately prior to the onset of the peritonitis. For example. Nordlund² noted preceding respiratory infections in 63 per cent of his patients; Schwartz,³ in 70 per cent; de la Chapelle,⁴ in 75 per cent; and Felson and Osofsky,⁵ in 100 per cent. Scarlet fever was associated with a primary streptococcie peritonitis in 20 cases collected from the literature by Sabadini.⁶ Bartone¹ added one, and we are adding three more, making a total of twenty-four cases of primary streptococcus peritonitis developing in the course of attacks of scarlet fever. A number of cases of streptococcus peritonitis have occurred during epidemics of septic sore throat,\* such as the milk-borne epidemic in Baltimore in 1912.⁰ Occasionally there is a preceding crysipelas,¹⁰ cervical adenitis,¹¹ retropharyngeal abscess, measles (authors), or any other condition in which a streptococcemia is present.

Scason.—Almost all streptococcus cases occur in the winter months, when other types of streptococcal infection are prevalent. Eighty per cent of Nordlund's 57 patients were admitted during the six-month period from December through May. Pneumococcal peritonitis, however, occurs approximately as often in summer as in winter.

Migration to Peritoneum.—Granted that the nasopharynx is the most common portal of entry, how do the bacteria reach the peritoneum? While a few authors<sup>12, 13, 14</sup> believe that the organisms are swallowed and then migrate through the wall of the intestine, especially in the ileocecal region, most authors<sup>2, 2, 5, 15, 16, 17</sup> believe that the bacteria reach the peritoneum from the nasopharynx through the blood stream. Duncan<sup>1</sup> feels that in his series of 67 cases, some must be classified under each of the above named routes. When one studies the clinical histories of most cases of streptococcus peritonitis occurring during scarlet fever, in which one first notes a tonsillitis followed many days later by a streptococcemia, and finally after many more days or even weeks by peritonitis, one is inclined to regard the hematogenous route as the most likely and frequent.

Sex.—Of all published cases of streptococcus peritonitis in which the sex is stated, 71 (33.8 per cent) were males and 139 (66.2 per cent) were females. In the pneumococcus cases there was an overwhelming preponderance (80 to 100 per cent) of females.<sup>1, 17, 18, 19</sup>

Age.—Nordlund tabulated 153 cases of streptococcus peritonitis according to age: 88 (57.5 per cent) were under ten years; 26 (17 per

<sup>\*</sup>There have been five bacteriologically proved cases and one presumptive case at the Willard Parker Hospital (1927-1936) out of a total of 11,669 scarlet fever admissions. Three of these have previously been reported by Kojis and McCabe.\* and the other three are included here.

cent), between ten and twenty; 22 (14.4 per cent), between twenty and thirty years; and 17 (11.1 per cent) over thirty years.

Mortality.—The mortality in streptococcus peritonitis is extremely high: 64 to 100 per cent in all the series reported.<sup>1, 12, 13, 15, 17</sup> This is even higher than in the pneumococcus variety, in which it is as low as 23 to 60 per cent in some series, <sup>1, 12, 18</sup> although some authors report a mortality of 100 per cent. The mortality is influenced considerably by age, as is well illustrated by Duncan, who had a mortality of 100 per cent in 11 children under three years of age, and of only 16 per cent in 6 children over eight years of age.

Diagnosis.-The diagnosis of peritonitis due to any of the pyogenic cocci depends on a careful consideration of the history, the physical examination, and the laboratory findings. There is almost always a history of sudden onset of severe, generalized abdominal pain and tenderness. Vomiting is an outstanding symptom, appearing early, frequently before the pain, persisting to the end, and uncontrollable. There may be hiccough. Abt<sup>20</sup> states that the cessation of the vomiting indicates walling off of the peritonitis. Diarrhea, often marked, is very common, although there is occasionally obstinate constination. The most constant finding in the physical examination is generalized abdominal spasticity and tenderness. Occasionally these may be very slight and localized, or entirely absent.1, 20, 21 There are consistently distention and tympany. In most streptococcus and staphylococcus cases and in occasional pneumococcus cases, there are symptoms and signs of an upper respiratory infection or of pneumonia preceding the onset of the abdominal complaints by several days or even by as long as two weeks. The temperature is between 103° and 105° F. in most instances. X-ray examination may show evidence of pneumonia and of intestinal dilatation. white blood count is consistently high (usually over 20,000 cells); the polymorphonuclear leucocytes are likewise considerably increased (usually over 85 per cent); and most important in the blood count is the marked "shift to the left," which is always present, even early in the disease (frequently over 50 per cent). The sedimentation rate is normal in almost all cases of acute appendicitis without perforation and is abnormal in all types of acute peritonitis.22

A definite clinical diagnosis of peritonitis cannot be made without operation or abdominal tap. The latter is very simple, informative and safe, as was made clear a decade ago by Neuhof and Cohen.<sup>23</sup> This procedure should be carried out in every case in which acute peritonitis in a child is suspected. Operation ought not be decided on until some information has been obtained from abdominal tap, if possible. In cases of acute peritonitis, such an examination, which takes only a short time, will occasionally save an ill-advised operation by demonstrating the type of organism on a smear of the fluid. If no fluid is obtained, the diagnosis of peritonitis is by no means ruled out. If a careful ex-

amination of the smear shows the presence of only streptococci or pneumococci, the case may temporarily, while awaiting the result of the culture, be considered a primary peritonitis and treated accordingly. Bacillus coli is present or if more than one type of organism is seen, then the case must be considered as a peritonitis due to a ruptured abdominal organ, most likely the appendix. Piercing the intestine with the exploratory needle is so extremely rare that the presence of the colon bacillus in the smear must be interpreted in the above manner. character of the fluid, aside from the characteristic coli odor, is of no value, as it is most variable in its physical properties. In attempting to distinguish clinically between streptococcal and pneumococcal peritonitis, it should be remembered that signs and symptoms of an upper respiratory infection or pneumonia speak for the former; a vaginal discharge or inflammation, for the latter. If the case occurs in the winter, especially when there are many streptococcus infections, or during an attack of scarlet fever, septic sore throat, erysipelas, cervical adenitis,11 or measles, it is probably of the streptococcus variety. patient is male, the peritonitis is almost surely not due to the pneumococcus. If the case is seen in the summer, it is probably not due to the streptococcus. Final differentiation depends on the bacteriologic examination of the abdominal fluid.

Treatment.-Since the mortality in all types of acute primary peritonitis is so appallingly high, the most important consideration, after the diagnosis has been established, is to give the patient the treatment most likely to save his life. Decision must be made either to operate or to wait. If acute appendicitis is suspected even after abdominal tap. immediate operation is the only choice. However, if the diagnosis of streptococcus or pneumococcus peritonitis has been definitely made, the question of operation versus purposeful delay must be considered. mediate operation, especially in the streptococcus cases, is recommended by many authors. 5, 6, 12, 15, 15, 15, 21, 28 Delay of one or several weeks is the method of choice, especially in the pneumococcus cases, according to many other writers.<sup>1, 16, 19, 29, 34</sup> Budde<sup>34</sup> recorded a mortality of 90 per cent in his cases of pneumococcus peritonitis operated upon during the first few days of the illness, of 33 per cent if there was a delay of over a week, and of 7 per cent if the delay was even longer. Lazarus35 stresses the point that operation should be performed either immediately or after several weeks, but not a few days after the onset of the illness, when the infection is spreading rapidly. Since streptococcus peritonitis has little tendency to localize,36 most patients with this disease are doomed no matter what is done surgically. Pneumococcus peritonitis has more tendency to localize, a fact that must be taken into account in deciding when to operate. Obadalek,12 whose mortality is the lowest of any large series in the literature, states that operation should be performed early in all eases, whether streptococcic or pneumococcic;

that drains should be used; that irrigation of the abdominal cavity should be done with large quantities of saline solution at operation, and sometimes later through the drainage tubes; and that the drains should be left undisturbed for ten days. Nordlund,2 whose series of fifty-seven streptococcus cases is the largest reported, says that in fulminating cases with a likelihood of sepsis, when the diagnosis of streptococcus peritonitis is certain, operation should be deferred; but that in milder cases, if early in the disease, and in cases in which the diagnosis is in doubt, operation should be performed immediately. Of 308 cases of primary streptococcus peritonitis reported in the literature (including the present series), there are records\* in 278 of whether or not operation was performed. Of the 278 cases, there were 44 recoveries, a mortality of 84.2 per cent. If one compares the result in the cases in which operation was performed with that in the cases in which operation was not performed, one sees a striking difference. Of 212 patients operated upon, there were 41 recoveries, a mortality of 80.7 per cent; and of 66 patients not operated upon, there were but three recoveries, a mortality of 95.5 per cent. The two groups are not entirely comparable, and as Duncan said, "It is not fair to draw conclusions as to the value of the nonoperative treatment . . . for many of them were so ill on admission that there did not appear to be any hope of saving them." Nevertheless, we feel that the difference in the mortality is great enough to make it clear that the treatment of choice, with Nordlund's reservations, is immediate laparotomy with drainage. The appearance of the peritoneal cavity at operation varies considerably, depending on how long the peritonitis has been present. Early in the disease, during the first twentyfour hours, the peritoneum and the serosal surface of the intestine. including the appendix, are congested and slightly edematous. There is usually a small amount of thin, turbid, yellow, serous fluid present. Later in the course of the infection, from the second to the fourth day, the serosal coat is covered with a fibrinous exudate; the congestion and edema are more marked; and the fluid is increased in quantity and is more purulent. After the peritonitis has been present even longer, there is a thick, plastic, fibrinous exudate covering the intestines; adhesions are usually present; and there is a larger amount of cloudy, yellow green. purulent fluid. At all stages the mesenteric and the retroperitoneal lymph nodes may be enlarged, firm and occasionally suppurating. pus has escaped from one of these glands into the peritoneal cavity, the case is not considered a primary peritonitis.

In addition to laparotomy there are other therapeutic measures which must be considered. Transfusions have been of little avail, but it is possible that in selected cases numerous small transfusions might be of benefit. Paralytic ileus should be strenuously combated, as in other

<sup>\*</sup>References 1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 15, 17, 19, 24, 25, 26, 28, 33, 37, 38, 39, 40 authors.

types of acute peritonitis, with continuous gastric suction, a rectal tube, turpentine stupes, colonic irrigation, pitressin, and prostigmin. recommend the trial of large doses of antipneumococcus or antistreptococcus serum or convalescent scarlet fever serum.41, 42 beginning as soon as the diagnosis has been made, although there has been no series of cases reported in which these biologic agents have been employed. As a result of animal experimentation, Smith43 believes that "the early therapeutic administration of (streptococcus) antitoxin should restrict tissue invasion." Rappaport and Brescia44 recently reported the cure of one case of pneumococcus peritonitis, which result they attribute to the use of large amounts of homologous antipneumococcus serum intravenously plus frequent transfusions. They recommend this procedure in addition to surgical intervention, and they give a review of the literature concerning the treatment of pneumococcus peritonitis. With the advances which are gradually being made in biologic therapy, this form of treatment, in combination with appropriate surgery, would seem to offer the greatest hope for the future.

# SUMMARY

- 1. Twelve cases of streptococcus and one case of staphylococcus primary peritonitis, occurring, with one exception, in children between the ages of two months and twelve years, are reported.
- 2. There was one recovery, and autopsy records of the other twelve cases are presented.
- 3. The close relationship between streptococcus infections of the throat and streptococcus peritonitis is pointed out.
- 4. The portal of entry in almost all cases of streptococcus peritonitis is the nasopharynx, and the bacteria reach the peritoneum through either the blood stream or the intestinal tract.
- 5. The diagnosis of peritonitis due to the pyogenic cocci is discussed, with especial emphasis on the importance of performing an abdominal paracentesis before considering operation.
- 6. The mortality in streptococcus peritonitis is approximately 85 per cent. With operation it is about 80 per cent and without operation over 95 per cent.
- 7. Energetic specific serotherapy, in addition to transfusions and infusions, with immediate operation in most streptococcus cases and delayed operation in most pneumococcus cases seems to offer the greatest hope in the treatment of primary peritonitis.

#### CASE REPORTS

## Following Scarlet Fever

Case 1.—S. B., a twelve-year-old female, was admitted to the Willard Parker Hospital on April 15, 1933, with a history of seven days' illness, starting with a sore throat, cough, fever, and a rash. The day before admission the patient com-

plained of generalized abdominal pain, nausea, and vomiting, and had fever. Physical examination revealed an acutely ill girl, with a fading scarlatiniform rash and some desquamation. The pharynx was acutely inflamed. Abdominal examination showed marked tenderness throughout, especially in the left lower quadrant; generalized rigidity; rebound tenderness; normal peristaltic sounds. Rectal examination was negative. The temperature was 102.8° F.; the pulse, 126; and the respirations, 24. The white blood count was 24,000; the polymorphonuclear leucocytes, 94 per cent. The urine was normal.

The admission diagnosis was scarlet fever with acute mesenteric lymphadenitis or generalized streptococcus peritonitis. The patient was carefully observed for the next thirty hours, during which time she seemed to get progressively worse. vomited green fluid several times. Severe abdominal pain persisted but was intermittent; and marked tenderness of the entire abdomen was consistently noted. temperature varied between 102° and 104° F.; the pulse, between 130 and 140; and the respirations remained at about 30 per minute. Blood culture was negative at the end of twenty-four hours. Operation was performed thirty hours after admis-The preoperative diagnosis was generalized primary sion under ether anesthesia. On opening the peritoneal cavity, a large amount of streptococcus peritonitis. yellow, seropurulent fluid was seen. The intestines were markedly injected and covered with a fibrinous exudate, and there was no perforation. A retrocecal appendix was found to be in the same condition as the intestines and was not gangrenous. It was removed and drains were inserted to the pelvis, upper abdomen, and appendix stump. The mesenteric lymph nodes were enlarged, but not suppurated. The other abdominal organs were normal.

Culture of the peritoneal fluid yielded the hemolytic streptococcus. The pathologist reported the appendix to be "inflamed secondarily to a general peritonitis."

Postoperative Course.—The temperature varied from 100° to 103° F., for three weeks; then from 99° to 101° F., for another two weeks; after which it remained normal until her discharge on the fifty-second day of her illness. The drains were removed on the fifth day postoperatively, and there was a moderate purulent discharge from the wound for five weeks. On the twenty-first postoperative day there was a sudden discharge of about 150 c.c. of pus, apparently coming from a deep abseess which drained through the abdominal wound. During the first ten days the child vomited occasionally, but after that she was symptomless. On the twenty-third day of the scarlet fever she developed an acute hemorrhagic nephritis. This gradually improved and by the time she was discharged, it was much less marked. This case is presented in considerable detail because of the rarity of recoveries in primary streptococcus peritonitis. The case is of especial interest because the surgeon, Dr. Edward McCabe, has reported another recovery in which he employed exactly the same procedure: removal of the appendix, drainage, removal of the drains on the fifth day.

Case 2.—L. C., a thirty-year-old colored female, was admitted to the Willard Parker Hospital on Feb. 14, 1933, with a history of seven days' illness, starting with a sore throat, hoarseness, and swollen glands of the neck. On the fourth day a punctate crythematous rash developed, and she had a temperature of 101.6° F.

Physical examination revealed a moderately ill, colored adult, with a punctate, erythematous eruption on the trunk, flushed skin, and desquamation of neck and chest. The pharynx and the tonsils were markedly congested; a mucopurulent exudate was present; there was an ulcer on the right posterior pillar. A mucopurulent nasal discharge was present. The abdomen was negative.

The admission diagnosis was scarlet fever. During the first eight days in the hospital the temperature ranged from 101° to 103° F., but no definite cause was

found for the fever. On the ninth day the patient became delinious. The lungs and abdomen were negative. The temperature rose to 104° to 105° F., and the white blood count was 36,200 cells, with 87 per cent polymorphonuclear leucocytes. The urine and the Wassermann test were negative. On the tenth day, an examination shortly before death revealed a "distended abdomen, apparently quite tender in the lower quadrants, especially the right." There were rales at both bases. There was no diarrhea A blood culture taken the day before death was later reported positive for hemolytic streptococci.

The final clinical diagnosis was toxic scarlet fever; streptococcemia.

Autopsy Report — The peritoneal cavity contained a large amount of thick, cloudy, brown fluid, in which some thick, white plaques of fibrin were found. The appendix, tubes, and ovaries had been removed (ten years previously). The mesenteric lymph nodes were moderately enlarged, but there was no suppuration. The gastrointestinal tract was intact. The pleural cavities each contained about 100 c.c. of thick, brown fluid with fibrinous plaques. The lungs showed marked confluent bronchopneumonia.

Cultures of the peritoneal fluid and of the blood yielded hemolytic streptococci.

The anatomic diagnosis was scarlet fever; streptococcemia; bilateral broncho pneumonia; bilateral empyema; acute generalized fibrinopurulent peritonitis.

CASE 3—E M. a two year old boy, was admitted to the Willard Parker Hospital
on March 31, 1936, with a history of five days' illness, starting with vomiting and
general malaise. The following day a rash and fever were noted, the next day sore
throat and misil discharge were piesent. The day prior to admission the neck
glands became swollen, and the temperature rose to 105° F.

Physical examination revealed a well developed, very ill boy. There was a moderately intense, punctate, crythematous rash on the trunk and extremities. The anterior cervical glands were the size of pigeons' eggs bilaterally. A profuse, scropurulent misal discharge was present. The tongue was "strawberry" in appearance. There was marked congestion of the pharynx and tonsils, which were enlarged and covered with an exudate. The liver and the spleen were both 2 finger-breadths below the costal margin. The heart and the lungs were normal. The temperature was 102° F, the pulse, 120; and the respirations, 24. The white blood count was 22,250; the polymorphonuclear leucocytes, 74 per cent, of which 27 were immature. The red blood count was 3,710,000, and the hemoglobin, 55 per cent. The admission diagnosis was scarlet fever; bilateral cervical adentis; hep itosplenomegaly.

Course in the Hospital .- On the fifth day the left eardrum ruptured spon taneously. A marked swelling and redness of the left thigh (at the site of a previous clisis) was first noted. Six days later a bilateral myringotomy was performed, and pus obtained from both ears. The culture of this pus yielded hemolytic streptococci. The abdomen was noted to be distended. Two days after this, there was severe ab dominal distention. The left ear was still draining pus, and there was now mustoid tenderness on this side. The swelling of the left thigh was diffuse and very tender. Although the child's general condition was very poor, an operation for a deep ab-cess of the thigh was decided upon. Under ethylene anesthesia, an incision into the thigh was made, and a large amount of thin, flaky pus was obtained after going through the fascia lata. More pus was obtained by making an in cision into the soft tissues over the lower end of the femur. At this point, the child censed breathing and could not be resuscitated. During the thirteen days in the hospital the temperature ranged from 103° to 105° P., and two blood cultures were negative. On the fourth day the white blood count was 25,000; the polymorpho nuclear leucocytes 95 per cent, of which 46 were immature.

The final clinical diagnosis was scarlet fever; bilateral cervical adenitis; sepsis; abscess of the left thigh; bilateral purulent otitis media; left mastoiditis.

Autopsy Report.—The peritoneal cavity contained about 300 c.c. of clear yellow fluid. The appendix was normal. The stomach and the intestines were markedly distended but not perforated. The mesenteric lymph nodes were prominent, pale, and not suppurating. In the lungs there were scattered areas of atelectasis. Cardiac Findings: The left ventricle contained a small amount of liquid blood and a clot, which extended into the orifice of the right coronary artery and for a short distance into the artery itself. The clot was not adherent to the ventricle wall or to the coronary artery. The spleen showed changes typical of an acute infection, as well as several recent infarcts.

Cultures of the peritoneal fluid, blood, mastoids, thigh, and larynx all yielded the hemolytic streptococcus.

The anatomic diagnosis was scarlet fever; dilatation of the heart; occlusion of the right coronary ostium by extension of ventricular clot; atelectasis of lungs; sepsis; bilateral mastoiditis; abscess of left thigh; generalized peritonitis.

## Following Measles

CASE 4.—D. F., a female, aged one and one-half years, was admitted to the Willard Parker Hospital on Feb. 6, 1933, with a history of coryza, discharging ears, a maculopapular rash, and a temperature of 105° F., since the day previous.

Physical examination revealed a small child, who was apparently moribund. temperature was 104.4° F.; the pulse, 170; and the respirations, 40. There was a maculopapular, erythematous eruption over the entire body. The conjunctivae were congested, and photophobia was noted. A mucopurulent nasal discharge was present. Koplik spots were seen, and the tongue papillae were hypertrophied. The pharynx was inflamed and edematous; the tonsils were hypertrophied, congested, and covered with mucopurulent exudate. There was marked cervical adenitis. Both cars were draining pus. There were a few râles at the bases of the lungs. heart sounds were of poor quality. The abdomen was markedly distended and tympanitic, but no tenderness, rigidity, or masses were noted. Ten thousand units of scarlet fever antitoxin were given, although scarlet fever was not suspected. A clysis and a transfusion were also given. The white blood count was 18,850; the polymorphonuclear leucocytes were 86 per cent. A blood culture was positive for the hemolytic streptococcus. The child had several watery, green stools; the temperature fluctuated from 103° to 107° F., and the child died about thirty hours after admission or within three days of the onset of the illness. The clinical diagnosis was measles; bilateral acute purulent otitis media; bilateral acute cervical adenitis; bronchopneumonia; streptococcus tonsillitis.

Autopsy Report.—The peritoneal cavity contained a large amount of clear yellow fluid. The visceral peritoneum was inflamed, and there was a fibrinopurulent exudate present over the small intestine. The appendix was normal. The mesenteric lymph nodes were very large and inflamed, but there was no suppuration. The gastro-intestinal tract showed no perforation. In the gastric mucosa there were numerous shallow ulcers with a hemorrhagic base, which appeared embolic in origin. The mucosa of the descending colon was acutely inflamed and studded with pinpoint ulcers. The anterior cervical and the mediastinal lymph nodes were enlarged and inflamed. The tonsils, larynx, vocal cords, trachea, and bronchi were congested and edematous.

Culture of the peritoneal fluid yielded a pure growth of the hemolytic streptococcus. The anatomic diagnosis was measles; streptococcemia; acute generalized peritonitis; acute tonsillitis, laryngitis, tracheitis, bronchitis; cellulitis of the neck; acute cervical, mediastinal, mesenteric lymphadenitis; acute ulcerative gastritis and colitis. CASE 5—V. M, a two year old female, was admitted to the Willard Parker Hospital on May 5, 1935, with a history of two weeks' illness. This started with an earache, which continued up to admission. Three days before coming to the hospital she had fever, the next day a rash on the face and a cough were first noted, on the following day the rash became generalized, there were lachrymation and a temperature of 102 f° F. Physical examination revealed a well developed young girl with a generalized, maculopapular rash, conjunctivitis, Koplik spots, congested pharyns and tonsils, and normal heart, lungs, and abdomen. The diagnosis was measles

The temperature on admission was 1014° F, and rose three days later to 104° F, Bilateral otitis media was diagnosed on the third day in the where it remained hospital, and the following day the child appeared very ill, with increased respira tory rate and bulging cardrums. The right eardrum was incised, and thick pus The white blood count was 22,250, with 85 per cent polymor was obtained An x ray plate showed a pleural effusion on the right phonuclear leucocytes The abdomen was distended. Two days later there were signs of a right upper lobe pneumonia, the right ear was still discharging; the left eardrum was subsiding, the abdomen was only slightly distended. On the next day there was marked abdominal distention, 150 cc of thin yellow pus was obtained from the right pleural civity, the chila died shortly after, on the thirteenth day of the mensles. The final clinical diagnosis was measles; right acute purulent otitis media; lob ir pneumonia, empyema, right

Autopsy Report —The peritoneal cavity contained about 100 cc of thin, middly fluid. The intestines were greatly distended. The appendix was slightly injected. There was moderate enlargement of the mesenteric lymph nodes but no suppuration. The right plant it exists was filled with green gray, thin, middly fluid. The right lung was solid and pale. The left lung had small areas of consolidation in the lower lobe.

Cultures from the peritoneal fluid, blood, right pleural fluid, and right lung all valded growths of Streptococcus hemolyticus and Streptococcus unidans

The anatomic diagnosis was measles, bilateral bronchopneumonia, empyema, right, sepsis, acute generalized peritonitis

CASE 6—R R, a three year old male, was admitted to the Willard Parker Hospital on March 10, 1936, after eight days of illness, starting with fever, cough, and vomiting. After two days the child was taken to a hospital, where physical examination and an array picture demonstrated a lobar pneumonia on the left side. For three days the temperature remained at about 103° F, but the child did not seem very ill. The Mantoux test was positive. On the fourth day in the hospital, a morbilliform rish and Koplik spots were noted, and the child was transferred to the Willard Parker Hospital. Physical examination revealed a well developed and nourished, moderately ill young boy, with an occasional cough. There were a few papular, crythematous lesions on the face. The conjunctival were congested, and there was a crusted nasal discharge. Many Koplik spots were seen. The tonsils were enlarged and congested. The heart and lungs were normal. The abdomen was described as flatulent but otherwise negative. The temperature was 103.4° F.; the pulse, 110; and the respirations, 24. The admission diagnosis was measured.

Three days after admission both eardrums ruptured spontaneously, and culture of the pus yielded hemolytic streptococi. The days after admission signs of consolidation of the entire left lung were present, and five days later empyema was diagnosed. Chest tap yielded 325 c.c. of green amber pus, which contained a pure growth of hemolytic streptococi. On the eleventh day in the hospital the right testicle became swollen, red and tender. This was thought to be due to orchitis. The abdomen was noted to be distended, and diffuse, marked tenderness was found

There was frequent vomiting, which, with the physical findings, suggested the possibility of acute peritonitis. The next day frequent soft, light stools were passed. For the next ten days the abdomen continued to be markedly distended and tympanitic, but there was only slight tenderness and no rigidity. The testis remained red, swollen, and tender. Chest taps continued to yield large amounts of thick, yellow brown pus. The temperature varied between 99° and 106° F., usually 101° to 104° F. On the fifth day in the hospital the white blood count was 16,000, with 89 per cent polymorphonuclear leucocytes; on the tenth day, 25,600 and 83 per cent; on the seventeenth day, 13,600 and 78 per cent. The child gradually grew weaker and died on the twenty-seventh day of measles.

The final clinical diagnosis was measles; acute bilateral purulent otitis media; lobar pneumonia of entire left lung; empyema, left; right-sided orchitis; generalized peritonitis (?).

Autopsy Report .- The peritoneal cavity contained a very large amount of thick, brown, muddy fluid under pressure. There were a few small, localized pockets of pus. The appendix was normal. The intestines were moderately distended, but there was no obstruction or perforation. The mesenteric glands were moderately enlarged, but not suppurating. The left pleural cavity was half filled with fluid similar to that in the peritoneum. The left lower lobe was firm and brown. the upper portion of a pncumonic process there was a small abscess filled with pus. Small abscesses, apparently of embolic origin, were identified on microscopic examination of both lungs. The tonsils were enlarged, inflamed, and contained several tiny pockets of pus. On microscopic section several necrotic areas with destroyed epithelium were found. In one necrotic area there was a blood vessel whose walls were necrotic and penetrated by bacteria. On opening the sac of the right testis, a considerable amount of pus escaped; this was in the tunica vaginalis; there was no apparent communication between it and the peritoneal cavity; the testis itself was not enlarged. The right mastoid contained a small amount of pus. The spleen showed the usual changes associated with a severe infection.

Cultures from the peritoneal cavity, blood, lungs, left pleural cavity, tonsils, larynx, right mastoid, and right tunica vaginalis all yielded pure growths of hemolytic streptococci.

The anatomic diagnosis was measles; acute purulent tonsillitis; streptococcemia; multiple embolic abscesses of both lungs; empyema, left; purulent periorchitis, right; right mastoiditis; generalized peritonitis.

### Following Scarlet Fever and Measles

CASE 7.—A.K., a female child, three and one-half years old, was admitted to the Willard Parker Hospital on May 30, 1931. She had had pneumonia at the age of one and one-half years. Four weeks before admission she had an illness which her physician diagnosed as measles, and one week before admission she again became ill, and her physician said that she had scarlet fever. Four days prior to coming to the hospital she vomited, had fever, pain in the chest, and was drowsy. There is in the history no mention of a rash.

Physical examination revealed a seriously ill young girl. She had a faint mottling (late measles?) over the entire body; desquamation in some areas (late scarlet fever?). The conjunctivae were injected and had a slight purulent discharge. There was some stomatitis; the tongue was coated and had enlarged papillae. The pharynx and the tonsils were moderately congested. In the lungs there were dullness, diminished bronchial breath sounds, and fine crackling râles over most of the left lung; slight dullness and bronchovesicular breath sounds were present in the right chest. The abdomen was negative. The temperature was 104.4° F.; the pulse, 150; and the respirations, 50. An x-ray plate confirmed the clinical

infant with rapid, grunting respirations and dilatation of the alae nasi. temperature was 1022° F.; the pulse, 156; the respirations, 56; and the weight, 12 pounds 7 ounces. The pharyna was slightly congested. The entire left chest was dull to flat posteriorly; the breath sounds were bronchial; there were no râles The right lung was normal. The liver was felt several fingerbreadths below the The following day the infant was moribund. The white blood cells costal margin numbered 35,300; the polymorphonuclear leucocytes, 79 per cent, of which 32 cells were immature. The red blood cells numbered 3,070,000; the hem oglobin content was 66 per cent. An aray examination revealed "evidence of pleural thickening in the outer zone of the left chest with some shaggy exudate and central consolidation in the region of the hilus and inner zone." There was no roentgenographic evidence of fluid in the pleural cavity. Nevertheless, the clinical signs of fluid were so clear that the chest was tapped in three places at the left base, but no fluid was obtained. The physical examination showed findings similar to those found on admission, except that the liver was faither below the costal margin. A transfusion of 120 cc. of citrated blood was given. During the next two days the status was essentially unchanged, with the temperature 103° to 104° F. abdomen was distended; gas was expelled through a rectal tube; the stools were loose but not frequent. The following day there were extreme dyspnea and cyanosis. Another cliest tap was done, but again no fluid was obtained. The abdomen was noted to be soft The temperature rose to 107° I., and the child expired on the fifth day in the hospital, or the eighth day of the illness.

The final clinical diagnosis was lobar pneumonia of the entire left lung; acute pharyngitis; acute enteritis.

Autopsy Report.—The peritoneal cavity contained some thin, watery, blood tinged yellow fluid. The stomach and most of the small intestines were dilated. The mesenteric lymph nodes were not suppurating. Empyema which practically collapsed the lung was present on the left side. The posterior visceral pleura was almost fused to the parietal pleura by a tenacious, fibrinopurulent exudate. The left lung filled to about one third its normal volume; it was consolidated and presented numerous small abscesses The right lung had scattered patches of depressed, purple Microscopically both lungs showed confluent bronchopneumonia with many small absecuses.

Culture of the peritoneal and pleural fluids yielded pure growths of Staphylococ cus aureus.

The anatomic diagnosis was consolidation of both lungs with multiple abscesses; empyema, left; acute generalized peritonitis.

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## LAURENCE-BIEDL SYNDROME

## CASE REPORT

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THE most constant phenomena of this familial symptom complex are adiposogenital dystrophy, night blindness, retinitis pigmentosa, mental deficiency, and anomalies of development, e.g., polydactylism and syndactylism. The following is a typical case of this syndrome:

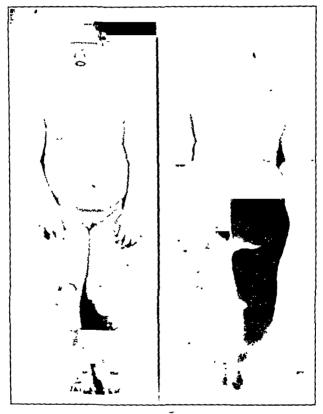


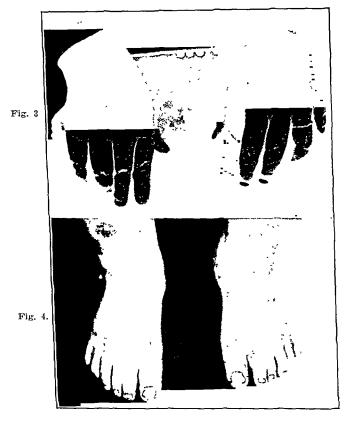
Fig. 1.

Fig. 2.

N. A., a white girl, aged twelve years, was referred to the pediatric dispensary because of obesity and poor vision. The mother had had three miscarriages. Both parents were well, and three older brothers were in good health. One brother died at the age of eighteen years with congenital heart disease. The patient's birth was normal and at full term. Nothing unusual was noted except polydactylism

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and syndactylism. She was breast fed for the first eighteen months of life. Dentition, so far as could be determined, was normal. She walked at the age of one year and talked at two years, but after this she progressed slowly. She became abnormally obese and had no desire to play with other children, although there was no gross disturbance of behavior. At six years she was started to school but had progressed no further than the third grade when seen in the dispensary at the age of twelve years. The parents attributed this to failing vision which they had first noticed six years previously. She could not distinguish articles held before her and ran into objects at night unless she was led. Physical examination revealed an obese girl of about normal height (137.5 cm., 55 inches) for her age



(Fig. 1). The weight was 61.4 kg. (135 pounds). The temperature and respiratory rate were normal. The pulse rate was 120 per minute. The blood pressure was 170 systolic and 80 diastolic. She was dull and obviously mentally retarded (estimated mental age of six years). The obesity was of the Fröhlich type (Figs. 1 and 2). The abdomen was protuberant with increase of girdle and suprapubic fat. The breasts were prominent; the proximal portions of the extremities were well rounded; and there was a marked degree of genu valgum and pes planus. Secondary sexual characteristics were absent. There was an extra digit on each hand (Fig. 3) and syndactylism and polydactylism of both feet (Fig. 4). Examination of the eyes showed no gross external defects but her vision could not be tested accurately because of poor cooperation. The peripheral fundi, however, showed discrete scattered splotches of pigment, dendritic in shape. There was beginning optic atrophy,

hyperphoria and considerable astigmatism. The retinal vessels were normal. The other findings were unessential. X-ray films of the skull and centers of ossification revealed normal conditions. The Wassermann and Kahn tests were negative.

#### COMMENT

Almost a hundred cases have been reported in the literature, and numerous hypotheses have been advanced concerning its pathogenesis since it was first described by Laurence and Moon in 1866.1 Biedl<sup>2</sup> felt that, since the roentgenograms of the sella turcica were normal, the syndrome was a familial form of adiposogenital dystrophy of cerebral rather than hypophysial origin. Raab's explanation of a dysfunction of the centers of the hypothalamus by an obstruction of secretion from the pars intermedia by a high or massive sella turcica is not logical since an abnormal sella is not present in the majority of cases reported. A more recent and plausible theory has been suggested on the basis of a hereditary developmental defect, involving two or more genes, bearing unit characters, that may carry simple recessives but not simple dominants.4, 5, 6

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# ACUTE NICOTINE POISONING

# REPORT OF A CASE IN A CHILD

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ACUTE nicotine poisoning has been recognized for many years and has been reported in the literature at infrequent intervals. Its occurrence in children has been referred to only in an occasional report, and an intensive review of all the pediatric periodicals fails to show a single reference to this clinical entity. The records of a large pediatric service for the past several years also fail to reveal a single previous diagnosis of nicotine poisoning.

The classical features of this condition have been described as sweating, nausea, vomiting, dyspnea, coma, convulsive seizures, pupillary changes, pulse rate first slowed and later accelerated, subnormal temperature and absence of tendon reflexes. These symptoms rapidly become more severe, and death follows in the majority of cases; or, in a few, the symptoms subside and the patient recovers completely in a few hours.

History.—S. H., a male white child, aged five years, was admitted to the ward on June 16, 1935, at 9:40 A.M., with a diagnosis of acute nicotine poisoning. A history obtained was that one hour previous to admission the child was given an enema consisting of 60 c c. of strong tobacco juice in 1,000 c.c. of water. Almost immediately after the injection the child became unconscious and vomited almost continuously. On admission the child was comatose and continued to vomit. The vomiting was nonprojectile in type and consisted of mucus. The family and personal history was irrelevant other than that the mother had noticed pinworms and the tobacco juice enema was a misdirected effort at medication.

Physical Examination.—On admission the pulse was 120, temperature 96° F. and respirations 45. The blood pressure was 90 systolic and 68 diastolic. Examination revealed an acutely ill child who was comatose and continuously moaning. The skin over the entire body was moist and cold. The pupils reacted sluggishly to light and were unequal, the left being slightly dilated. Respirations were shallow and rapid. Heart rate was 120 per minute, of regular rhythm, and the sounds were of fair quality. Neurologic examination revealed sluggish reflexes throughout.

Laboratory Data.—The blood count showed white cells 10,300, red cells 5,120,000, and hemoglobin 90 per cent. The differential count was 88 per cent neutrophiles and 12 per cent lymphocytes. The blood Kahn reaction was negative. The Mantoux test was negative. The urine showed a trace of albumin, which was absent on subsequent examinations.

Course.—On admission caffeine sodium benzoate was given and repeated every thirty minutes for three times. External heat was applied, and copious enemas were given in an effort to eliminate the nicotine. The child regained consciousness in about one hour and appeared almost well in two hours with a normal temperature, pulse, and respiration. The child was dismissed on the third hospital day as completely recovered.

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#### REVIEW OF LITERATURE

A review of the literature reveals the majority of the cases of nicotine poisoning to be in adults. Franke and Thomas, in a recent report, were able to find seventy-four fatal cases of nicotine poisoning. The large majority of these cases were reported in the foreign literature and covered a period from the middle of the seventeenth century to the present time. Of these cases twenty-eight were from concentrated solutions of nicotine and forty-six from tobacco poisoning.

McNally<sup>2</sup> reported several fatal cases the result of mistaking insecticides for whiskey. Lockhart<sup>3</sup> reports severe poisoning in a girl employed in the manufacture of a nicotine insecticide. Two drams of a 95 per cent solution of nicotine was spilled on the sleeve of her overalls. She immediately removed the overalls, washed her arm, wiped off the sleeve and returned to work. Twenty minutes later she collapsed, was cold, pallid, and speechless. She appeared for thirty minutes to be on the verge of death but finally recovered.

Faulkner' reports the case of a florist who sat down in a chair on which had been spilled "Nico-Fume Liquid." Fifteen minutes later the patient presented the usual symptoms of nicotine poisoning and remained unconscious for three hours. The patient was given the same clothes on leaving the hospital four days later and was again seized with symptoms of nicotine poisoning in a few hours, but not nearly so severe. Besides the usual classic finding, Faulkner describes electrocardiographic changes suggesting myocardial damage in his case. Fretwurst and Hertz' demonstrated an increase in blood sugar and a leucocytosis in cases reported by them.

In reviewing the literature more thoroughly for the occurrence of nicotine poisoning in children, we find only a few cases reported. Me-Nally refers to the three cases reported by Weidanz with death in one and serious illness in two others, the result of tobacco's being sprinkled on the skin for treatment of favus. He makes reference to another case by Merrian resulting from application of a decoction of tobacco used in the treatment of ringworm of the scalp. McNally also mentions a case reported by an undesignated author in which an infant aged three years blew soap bubbles for one hour with a pipe and died on the third day. All the above cases in children were reported in the eighteenth century.

Bleasdale<sup>7</sup> reports a case similar to our own, in a child two years old who had been given a tobacco decoction rectally for the cure of intestinal parasites. This child presented the usual symptoms of a very serious character but recovered after artificial respiration had been administered for one hour.

The most recent reference to this condition in children is by Reynolds<sup>8</sup> in 1914. He reported the case of a five-month-old infant who was fed from a bottle into which tobacco had been accidentally dropped while

preparing the formula. The child was kept alive for some time by alternating periods of artificial respiration but died in one of the periods when his condition seemed favorable. As far as we can ascertain, only eight cases of nicotine poisoning have been reported in children, including the case in this paper.

## DISCUSSION

The infrequency of acute nicotine poisoning as a diagnosis is remarkable since tobacco is so commonly used. Nicotine, a liquid alkaloid, is the chief poisonous principle of tobacco. It has been estimated that one cigar contains enough nicotine to kill two persons if injected into the circulation. Tobacco contains from 2 to 7 per cent nicotine.

Acute nicotine poisoning, until the investigative work which has been published by Franke and Thomas, was considered an almost hopeless condition. The belief has heretofore been prevalent that death was due to a generalized paralysis of the central nervous system. It has been definitely shown by the above investigators that death from acute nicotine poisoning is due to peripheral paralysis of the respiratory muscles when convulsions are prevented, and if these occur, to fixation of the respiratory muscles. Gold and Brown<sup>10</sup> also have recently published evidence that shows a peripheral rather than central paralysis.

Langley and Dickinson<sup>11</sup> showed many years ago that animals could be kept alive by artificial respiration after administration of what would otherwise be a fatal dose of nicotine. However, this work was not sufficiently publicized to cause adoption of this simple procedure as a definite therapeutic measure in acute nicotine poisoning of the human being.

Franke and Thomas¹ in a recent publication emphasize very strongly that artificial respiration started before the circulation has failed and continued until the muscular paralysis passes off should prove uniformly successful. They also have done experimental work showing a good possibility of restoring the circulation soon after it has failed, by injection of epinephrine into the left ventricle.

## SUMMARY

Although acute nicotine poisoning appears to be a relatively rare disease, the frequent exposure of children to tobacco in the American home makes it a clinical entity with which every physician should be familiar.

The possibility of acute nicotine poisoning should be strongly considered in all cases of undiagnosed coma. An attempt to clicit a history of contact with nicotine should always be made in these cases, for there is a possibility that many of these cases have occurred with a failure of diagnosis.

The classical experiments mentioned have established the definite therapeutic value of artificial respiration and the injection of epinephrine in cases where the heart has stopped beating.

It might be suggested that the mechanical respirator would furnish the ideal method of carrying on respiration in these cases until the temporary paralysis of the involved respiratory muscles has subsided.

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# EXPERIMENTAL VACCINATION AGAINST COLDS IN AN INFANTS' HOME

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THE reduction of the incidence of catarrhal infections of the upper respiratory tract in institutions for the care of children resolves itself into three lines of action: first, prevention of entrance of infection; second, preventing its spread; and third, increasing the power of resistance of those exposed. The first two methods are somewhat difficult (in spite of isolation) in view of frequent admissions and contact with the outside world, whether in the play yard or with visitors. In view of the foregoing, the third step, that of increasing the resistance, becomes more important, and vaccine was turned to as the easiest method available.

Colds were formerly believed to be due to the pneumococci, streptococci, influenza bacilli, and other organisms commonly found in the upper air passages. The causative agent is now looked upon as a filtrable virus, 1-4 which very often may be accompanied by secondary invaders (pneumococci, streptococci, influenza bacilli). Kneeland<sup>5</sup> found, in children afflicted with colds, a rise in the carrier rate of pathogenic organisms corresponding to an increase in the severity of the infection.

Vaccination against colds has been used for many years, both in adults and children, in the belief that it was directed against the specific agents. The vaccine may operate in a specific way to immunize against these secondary invaders, and may, second, as a nonspecific foreign protein, increase the general resistance of the body against infection. Such vaccination against colds was carried out at the Infants' Home of Brooklyn with the hope of reducing the susceptibility to colds and possibly modifying the course of the attacks.

The results of such experiments as have been reported in the literature are by no means decisive. The statistics of some authors show no effect; others show a slight relief, and the rest are noncommittal. W. H. Park and von Sholly immunized 1,536 persons during 1919-1920 and gave three injections at weekly intervals. The vaccine was reported as having little value in preventing colds but as having a slight effect on their severity. Jordan and Sharp used the same vaccine and technic as Dr. Park on 6,066 people in Florida and found almost the same frequency of rhinitis and bronchitis in the vaccinated and nonvaccinated groups. They stated that the pneumonia and influenza rates were somewhat lower among those vaccinated, but the difference was not great.

From the Infants' Home of Brooklyn and the Department of Laboratories, Israel-

In 1927 Ferguson, Davey, and Topley,<sup>s</sup> of Manchester, England, injected a group of 138 persons with three doses of vaccine at weekly intervals, using a slightly different type of mixture than that of Dr. Park. The English vaccine contained: M. Catarrhalis, 200M; Friedländer's bacillus, 200M; B. septus, 200M; B. hoffmannii, 200M; mixed staphylococci, 200M; Pfeiffer's bacillus, 120M; pneumococci, 40M; streptococci, 40M. The American vaccine in 1920 contained Pfeiffer's bacillus, 500M; hemolytic streptococci, 500M; Streptococcus viridans, 500M; pneumococcus type 1, 1,000M; type 2, 1,000M; type 3, 500M. Their results show a very slight decrease in the severity of the infection as measured by duration, days in bed, and days away from work, but they found no justification for the use of stock vaccines, as were available, in the hope of lessening the frequency of the common cold.

During the winter of 1929-1930, Brown<sup>9</sup> gave twelve doses of a specially prepared vaccine to medical students at the University of Cincinnati. He worked out a most thorough plan of preparation, including age, height and weight tables, past history of upper respiratory infections, environment, clothing and diet. Skin tests were also done, using each component of the vaccine as a separate antigen. The conclusion was that the statistical results showed little, if any, improvement as regards common colds in the experimental group as a whole compared with the controls.

Similar work has been carried out in Europe in children's homes and hospitals, by Stoltenberg, 10 at Oslo, and Gyllenswärd, 11 at Copenhagen. Both gave three injections at five-day intervals, using a vaccine containing pneumococci, streptococci, M. catarrhalis and Pfeiffer's bacillus. Stoltenberg injected 487 children and had 496 controls. His results show a beneficial effect among the vaccinated as compared with the non-vaccinated: per cent attacked, 47.9 nonvaccinated, 20.12 vaccinated; number of infections, 438 nonvaccinated, 118 vaccinated; index infectiosus (number of infections per child per hundred days), 1.73 nonvaccinated, 0.73 vaccinated.

Gyllenswärd, on the other hand, reported on 122 injected children and 125 controls and concluded that there were no great differences in the number of children ill, the number of recurrences, duration of illness, or frequency of complications.

Kneeland<sup>12</sup> injected twenty-three children at a Home for Infants in New York, giving two courses, one in October and the second in February, nine and seven doses, respectively, at weekly intervals. The vaccine contained pneumococcus type 1, *H. influenzae* and hemolytic streptococci in the ratio of 5:3:3. The number of individual respiratory infections were 5.4 in the vaccinated group and 5.8 in the controls. There was an alteration in the severity, as measured by the number of days of fever that occurred, even though no difference in the number of infections was noted.

# SCOPE OF EXPERIMENT

The Infants' Home of Brooklyn is a permanent home for children from birth through six years of age. They are classified as infants up to one year, toddlers up to two and a half years, and older children up to six years.

All newly admitted children are quarantined for three weeks in glass-walled cubicles in the admitting ward, with individual nursing technic. Routine nose and throat cultures are taken, and vaginal smears are made. The rest of the children are housed in open dormitories, according to age groups, males and females being separated only in the older division. The total resident population during the two years covered by the experiment was 60 in 1933 and 80 in 1934.

The group chosen for injection was made up of those children with past histories of frequent colds and upper air passage involvement. Controls were chosen in each of three age periods. No change was made in the normal routine, the diet remained the same, cod liver oil was given to the infants, and the outdoor play period under the supervision of the kindergarten staff was continued.

The injections were begun in October of each year, one course of eight subcutaneous injections was given semiweekly. The initial dose was 0.1 c.c. and was increased gradually up to 1.0 c.c., a total of 4.6 c.c. per child. Parke, Davis and Company catarrhal vaccine, combined (called "vaccine B" in the paper), was used in 1933. This contains Friedländer's bacillus, 50M; pneumococci (4 types), 100M; M. catarrhalis, 50M; Streptococcus hemolyticus and Streptococcus nonhemolyticus, 100M; Staphylococcus albus and Staphylococcus aureus, 700M; pseudodiphtheria bacillus, 100M; B. influenza (Pfeiffer), 100M.

The following year a nonspecific vaccine (called "vaccine A") obtained from saprophytic air bacteria was used as well as the Parke, Davis vaccine. The vaccine A was furnished through the courtesy of Dr. L. Rosenthal, director of laboratories of the Israel-Zion Hospital.

The period of observation lasted for one year in each experiment: all temperatures over 100° F. were recorded, as well as type and number of upper respiratory infections. Several children were discharged from the institution during the year and were excluded from the tabulations—24 injected in 1933 with 5 exclusions and 40 injected in 1934 with 6 exclusions. Two adult staff members were injected but were not included.

Skin tests were done by giving the first dose intradermally. There were only a few positive reactors, but, as the vaccine is a combination of bacteria, individual type sensitivity could not be determined.

#### RESULTS

Tables I and II show the number of days of temperature over 100° F. in each age group during the first year, 1933-1934, for nineteen vaccinated and control children, respectively. These are represented graph-

TABLE I

NUMBER OF DAYS OF TEMPERATURE OVER 100° F.-VACCINATED GROUP, 1933-1934

AVERAGE	13.2	5,57	3.57	6.84
ANNUAL	99	33	53	130
SEPT.	9	0	ø	14
VOO.	11	~	m	21
זמויג	-		0	8
JUNE	t~	0	دء :-	10
хүк	c1	0	63	431
APR.	6	ເລ	0	17.
MAR.	F	0	0	==
FEB.	000	15	¢1	153
JAN.	5	H	ນ	13
DEC.	0	0	C1 .	0.1
NOV.	0	0	0	0
ocr.	0	0	0	0
NO.	່ເວ	۲-	~	19
AGE IN YEARS	0.1	1.21/2	9.5/6	Total

TABLE II

NUMBER OF DAYS OF ТЕМРЕВАТИН ОVER 100° F.--Сомтиол Group, 1953-1934

MEAN	24.28	15.1	5.86	14.26
ANNUAL	124	100	41	271
SEPT.	21	9	ന	30
AUG.	30	21	0	51
JULY	4	0	-	5
JUNE	10	0	63	15
AVK	33	က	<u>-</u>	13
APR.	95	<del>-1</del> 1	90	35
MAR.	5.5	6	0	12
FEB.	15	2	<u>н</u>	23
JAN.	2	15	12	34
DEC.	5	7.		50
NOV.	7.	~	4	15
ocr.	C.3	2	63	14
NG. INJECTED	3	۲-	7	19
AGE IN YEARS	0-1	7.2%	21/2-6	Total

TABLE III

NUMBER OF DAYS OF TEMPERATURE OVER 100° F.-NONSPECIFIC VACCINE A GROUP, 1934-1935

, ii	1					l
MEAN	1					1
ANNUAL	00	9	22		30	204
SEPT.	-	>	ıc	,	<del>, ,</del>	9
AUG.	6	1	_	,	0	67
JULT	9		œ	,	0	14
JUNE	-	4	c	,	0	-
MAY	7		<del>, ,</del>	١,	-	6
APR.	-	•	0	,		22
M.AR.	c	,	တ	,	27	8
FEB.	9	,	~	•	4	17
JAN.	2.4	1 4	83	,	` ?	63
DEC.	20		25	,	27	62
NOV.	21	! !	m	٠	77	26
OCT.	0	•	>		0	0
NO. INJECTED	ιΩ	,	9	٠	0	17
AGE IN YEARS	0-1		₹.?.T	01/10	7.77	Total

TABLE IV

NUMBER OF DAYS OF TEMPERATURE OVER 100° F.—VACCINE B GROUP, 1931-1935

NAGAR	Name of the last	AVERAGE	800		13.5	6.16		12.53			
	ANDANA	TOTAL	5		5	246	-	010	1		
	шалы	1775	6	1	_	• •	>	c	J		
	0114	300	٥	•	17	0 0	:1	1	2		
	*****	3106	t	_	10	1	0		F		
	10000	TONE	,	-1	_	<b>D</b> (	21	۶	0		
		MAY	1	_	+	٠,	0		-1		
		APR.		c.	1 9	<del>-</del>	ເລ		9		
		MAR.		Ŀ	- (	33	C.		<u>.</u>	-	
		FEB.		5	Ţ	0	_	,	6	7	
		JAN.		١	S	o;	) C	OT.	65	90	
		DEC.		1	20	30	1 7	2	90	27	
		NOV.	:		_	ĸ	•	>	۱	77	
		J. J.	;		0		<b>-</b>	0	1	<b>5</b>	
		NO.	INTECTED	-	٤.	۰ د	٥	ဗ		17	
		NI 30Y	100	CAVAI		1.0	1.21/2	9.716	2 2	Trotal	

TABLE V

NUMBER OF DAYS OF TEMPERATURE OVER 100° F.-CONTROL GROUP, 1934-1935

MEAN AVERAGE	29.6 16.3 7.83	17.23
ANNUAL	148 98 47	293
SEPT.	0110	es
AUG.	5 4 0	6
AIOF	11 27 6	#
JUNE	13 0 4	17
MAY	10 1	11
APR.	14 7 2	23
MAR.	13 C	6
FEB.	22 7	30
JAN.	23	62
DEC.	29 18 26	73
NOV.	0 H 03	12
OCT.	000	0
NO.	0 0	17
AGE IN	0-1 1-2½ 2½-6	Total

ically as monthly totals for all ages in Fig. 1. The vaccinated group had 130 days of fever (temperature over 100° F.); the controls had 271 days. This difference is similarly reflected in the separate age groups: infants, 66 days; toddlers, 39 days; older, 25 days among the injected children, as compared with 124, 106, and 41 days among the respective

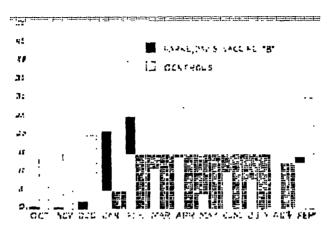


Chart 1.—Monthly total of days with temperature over 100° F, for all age groups, 1934-1935.

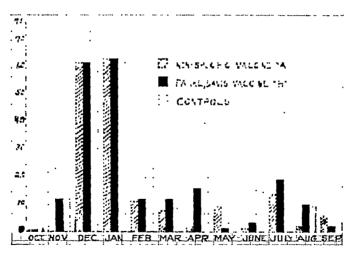


Chart 2.—Monthly total of days with temperature over 100° F. for all age groups, 1934-1935.

controls. The average number of days of fever per child was 6.84 for vaccinated groups and 14.26 for the control groups.

Tables III, IV, and V represent the results of the second year, 1934-1935, for vaccine A, vaccine B, and control groups, respectively. During the winter months of 1934-1935, there was a particularly severe epidemic of upper respiratory infections which raised the total days of

fever considerably over that of the preceding year. There was very little difference between the nonspecific vaccine A and vaccine B, 204 and 212 days, while the control group had 293 days of fever. The monthly totals are shown in Chart 2. The average number of days of fever per child for the year was 12 for vaccine A group, 12.52 for vaccine B group, and 17.23 for the untreated control group.

Tables VI and VII show the number of colds for each age group during the two years and the index infectiosus. This index was described by Stoltenberg<sup>10</sup> and is defined as the number of infections per child per hundred days. There was an appreciable, though slight, difference between vaccinated and unvaccinated control children during the first year, 1933-1934, with 37 colds as compared with 52 colds, respectively, and a rise in the combined index infectiosus for all age groups from 0.534 in the experimental to 0.75 in the control children.

TABLE VI Number of Colds and Index Infectiosus, 1933-1934

193	3-1934	VACC	INE B	CON'	TROLS
AGE IN	NO.	NO. OF	INDEX	NO. OF	INDEX
YEARS	INJECTED	COLDS	INFECT.	COLDS	INFECT.
0·1	5	19	1.04	20	1.09
1·2½	7	10	0.39	24	0.939
2½·6	7	8	0.31	8	0.31
Total	19	37	0.534	52	0.75

TABLE VII

NUMBER OF COLDS AND INDEX INFECTIOSUS, 1934-1935

1934-	1935	VACC	INE A	VACC	INE B	CONT	ROLS
AGE IN YEARS 0-1 1-2½ 2½-6 Total	NO. IN- JECTED 5 6 6	NO. OF COLDS  13 14 6 33	0.717 0.685 0.274	NO. OF COLDS 13 14 8	INDEX INFECT. 0.717 0.685 0.365 0.564	NO. OF COLDS 19 14 10 43	INDEX INFECT. 1.04 0.685 0.456 0.693

The gap between the two groups was not so marked during the second year, however, the total number of colds being 33 for the vaccine A group, 35 for the vaccine B group, and 43 among the control group. The combined index infectiosus rose only slightly from 0.531 and 0.564 for vaccines A and B groups, respectively, to 0.693 in the control series.

# DISCUSSION

The results of the two-year study period show the variations obtainable in the use of vaccines for prophylaxis against colds. During 1933-1934, there was a reduction of 52 per cent in the number of days of fever in the vaccinated group and almost 29 per cent less colds. This coincides with the favorable results reported by Stoltenberg<sup>10</sup> from Oslo

and by Kneeland12 in New York. Ernberg,13 in discussing Gyllensward's work, stated that he had good results with Parke, Davis and Company vaccine used on 49 nurses, but gave no figures.

The results of the second year, 1934-1935, were not so favorable as those of the preceding period. There was almost no appreciable difference in the number of days of fever or the number of colds between the nonspecific vaccine A and the vaccine B. The noninjected controls showed an increase of 29 per cent in the days of fever and had almost 21 per cent more colds. This bears out the contention of several investigators that the number of days of fever was decreased, i.e., the severity was lessened, but the actual number of colds showed only a slightly appreciable change.

It is possible that better results may be obtained by increasing the dosage of the vaccine, but more improvement might result by using the particular antigen to which the children are sensitive.

#### SUMMARY

Vaccination against upper respiratory infections (colds) was attempted at an infants' home over a two-year period, from 1933 to 1935, 19 children being injected the first year and 34 the second. There was a definite decrease in the severity of the infections, as measured by the number of days of temperature over 100° F., but only a slight reduction in the actual number of infections.

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1650 OCEAN AVENUE

# THE SIGNIFICANCE OF AND A DIFFERENTIAL DIAGNOSTIC TEST OF PRECORDIAL MURMURS IN CHILDREN

MARTIN M. MALINER, M.D., BROOKLYN, N. Y., AND IRVING OKIN, M.D., PASSAIC, N. J.

CINCE the invention of the stethoscope by Laennec in 1819, the ques-Ition of the importance of precordial murmurs has disturbed the mind of many a clinician. At first it was agreed upon that the murmur represented a serious pathologic cardiac condition and meant a lifelong period of invalidism. However, since it developed that many of these foredoomed individuals persisted in maintaining a rather protracted hold on life, and often indulging in a strenuous one, a need for reconsideration of murmurs was in order. As is usual when a new school of thought makes its début, extremes express the changing order: thus it has been declared that a cardiac murmur per se meant absolutely nothing. MacKenzie1 often advised throwing the stethoscope away! Cabot stated that a systolic murmur without other signs of heart disease was of no importance as evidence of valvular lesions. The majority of present-day physicians have been following this trend of thought. The New York Heart Association in its "Criteria for the Diagnosis of Heart Disease''2 specifically insists that a patient with a murmur and without other distinctive concomitant findings is to be grouped in Class E (functional heart disease).

More recently, however, a number of observers have become less adamant and are recognizing the probability that many so-called functional heart cases are truly organic. Smith3 recommended that every heart with a murmur be examined at periodical intervals in order to detect other possible evidences of heart involvement as the years pass. Freeman and Levine4 in a study of one thousand consecutive noncardiac cases concluded that a systolic murmur of greater intensity than grade 2 should be regarded with suspicion. Fineberg and Steuer,5 in a followup study of one hundred children with an uncomplicated systolic apical murmur, discovered that 30 per cent developed serious valvular complications within a period of five years. Friedlander and Brown<sup>6</sup> in a very recent study felt that the louder murmurs are probably associated with organic cardiovascular disease. Levine' frankly states that all systolic murmurs need consideration and that the louder ones are always associated with some form of cardiovascular disease. White8 also agrees that the louder the murmur, the more likely it is to be organic. As a result of all these studies, the murmur is beginning to receive greater

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consideration. We all concur with Simpson and Batten, who say that murmurs are responsible for more troubles and difficulties than all the other cardiac signs put together.

If one were to acquiesce in the belief that the mere presence of a murmur is of no significance, then our procedure is simple, namely, to ignore it and the patient. But if we accept the plea of the authors that an early insidiously developing rheumatic infection of the heart may present no other evidence except a precordial murmur, the importance of recognizing the true nature of this murmur is not so much a matter of declaring the individual so afflicted a "cardiac," but rather, in acknowledging that a rheumatic heart means greater susceptibility to reinfection. Only with this understanding will a greater effort be expended in classifying properly the child with a murmur. This will result in the very early diagnosis of a treacherous condition and will be helpful in preventing subsequent morbidity and precocious mortality.

If a method or means were devised to differentiate the so-called functional murmur from the truly organic one, an important aid will be given both the physician and the patient. Many characteristics have been ascribed to distinguish one from the other, but we are in accord with Morse, '0 who says, 'There is no certain distinction between organic and functional murmurs.' Morison' described the use of amyl nitrite inhalation as a means of accentuating and so differentiating murmurs. However, Kahler's results using similar methods were completely the reverse, and, as will be seen later, our own experience with amyl nitrite is more in accordance with that of Kahler. Bass, Mond, Messeloff and Oppenheimer' have made use of a phonocardiograph to differentiate the two types of murmurs, but this method appears somewhat complicated for general use.

Five years ago one of us14 devised a means of accentuating and localizing cardiac murmurs by the use of a subcutaneous injection of epineph-At that time 62 children of the cardiac out-patient rine 1:1,000. department were tested. Of this number, 32 were considered clinically as having functional or Class E murmurs. Following the epinephrine test, 23, or 71.2 per cent of the cases so tested, were considered as definitely presenting an underlying organic cardiac condition and not functional as was presupposed. The character of the murmur, rather than the accepted criteria was the basis for this conclusion. It was the oninion of the writer at that time, and it is now our belief, that there is a stage in organic valvular heart disease of children in which there is no visible hypertrophy of any of the heart chambers and in which there are none of the conditions usually associated with a well-established valvular lesion. This period may be of variable duration depending upon many factors: the virulence and progression of the infecting agent, the number of recurrences of the infection, the individual resistance, and the cardiac response of the child afflicted. In our estimation a fairly loud

precordial murmur with maximum intensity at or near the apex and transmitted over the precordium or toward the axilla is indicative of an underlying organic valvular condition.

Levine divides murmurs into six grades according to intensity. The first two groups, he claims, are almost always noneardiac, the remaining four grades being usually organic. We prefer, for the sake of simplicity, to arrange the murmurs into three groups according to intensity. Those that are either faint or very soft are most likely functional; the moderately loud and the very loud comprise the second and third grades, respectively. These latter two we consider always organic, even in the absence of other criteria. When the epinephrine caused a faint or very soft murmur to appear, the case was placed in group 1 and considered nonorganic; when placed in group 2 or 3, the case was considered organic. Frequently a fairly loud murmur appeared localized at the second left interspace; this was also considered as being functional.

TABLE I

PATIENTS TESTED FIVE YEARS AGO, WITH EPINEPHRINE DIAGNOSIS THEN,
AND CLINICAL DIAGNOSIS NOW

	1931		193	G
NUMBER TESTED	MURMUR LOCALIZED TO BASE OR DIMINISHED	MURMUR INCREASED NEAR APEX	CLINICAL HEART DISEASE	PER CENT OF PREDICTED HEART DISEASE
32	9 (28.2%)	23 (71.8%)	11 (34.3%)	47.8%
	Cases	Tested in New G	roup, 1936	
37	14 (37.9%)	23 (62.1%)	to develop de disease withi	, number expected finite organic heart n 5 years 47.8%)

Five years have elapsed since the epinephrine test was performed on the original group of thirty-two children with a clinical diagnosis of functional cardiac disturbance. The purpose of this paper is, first, to follow up the clinical condition of this group of children and, second, to test a new group of similar cases. A percentage of the new group was given a preliminary test with amyl nitrite. as described by Morison, before proceeding with the epinephrine.

Of the original group of 32, the present diagnosis in accordance with accepted criteria shows that of the 9 patients in whom the diagnosis remained as functional or Class E after the epinephrine test, 5 are still elinically Class E: 3 have been discharged as noncardiac; and one child has been lost to the records. Of the 23 children in whom the epinephrine diagnosis was organic valvular heart disease, today 9 are still considered as being elinically in Class E and 11 have a definite valvular defect; the remaining 3 have been lost track of. This means that 47.8 per cent of an original group of 23 children with a so-called elinical functional precordial murmur have, within a period of five years, developed typical

organic valvular heart defects. According to Chart 1, in the children under ten years of age the clinical findings five years later do not completely bear out the epinephrine diagnosis, but, in the children over ten, the test appears to be 100 per cent correct. Up to and including ten years, 15 cases were called organic and 2 Class E after the test; five years later 5 are clinically organic while 14 are still being classified as functional. However, this does not necessarily mean that these children do not have an organic valvular defect. In the first place, it is rather difficult to concede that a precordial murmur present for five years is entirely accidental, and, second, it is a well-known fact that the rheumatic states may be dormant for many years only to appear at some indefinite time. Continued observation will offer the only certainty. There is one point we wish to mention: in our out-patient department

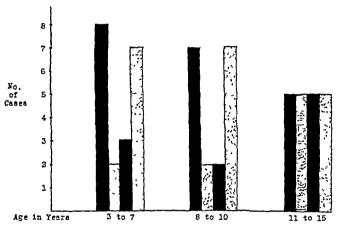


Chart 1.—Class I cardiac children tested with epinephrine, showing the diagnosis following the test and the chinical diagnosis five years later.

The solid columns represent the organic cases and the stippled columns, Class E cases. The first two columns show the diagnosis after epinephrine and the second two columns, the clinical diagnosis five years later.

the child is first examined in the general clinic, and, if a faint murmur is noted at the base, the child is not referred to the special clinic. This necessarily climinates a very large group of functional murmurs.

#### PROCEDURE

Thirty-seven children clinically in Class E, according to the criteria of the New York Heart Association, were selected for this study. Twelve of these were given the preliminary amyl nitrite test. The ages of the children varied from five to fifteen years; 22 were under ten years old, and 15 were ten years old or over. For comparative purposes, a group of 15 children with a clinical diagnosis of organic heart disease was also given the test. All were tested about two hours after breakfast. No child having a rectal temperature over 100° F. or who appeared to be

ill was included. The patient was placed in the recumbent position and the pulse and blood pressure taken. The precordium was then auscultated for heart sounds and murmurs. Epinephrine 1:1,000 was injected into cither deltoid region, the patient remaining in the recumbent position throughout the test period. The child under eight years received 6 minims, the older child, 8. Immediately following the injection and every five minutes thereafter, the pulse, blood pressure readings, and auscultatory findings were recorded (Table II). Variations of the murmur in quality, intensity, duration, and location were noted. This examination was continued for a period of thirty minutes. The maximum effect of the drug occurred from ten to twenty minutes after the injection. At the conclusion of the period each child was able to go home feeling perfectly well. No deleterious effects were observed in any case. In the twelve children receiving the amyl nitrite, a 3 minim perle was crushed and held over the child's nostrils for a few seconds until physiologic changes, such as flushing and rapid pulse, occurred. Observations similar to those following the epinephrine were made, but these had to be done immediately because of the evanescent action of this drug. With the return of the pulse and blood pressure to normal, which usually occurred within a few minutes, the subcutaneous epinephrine test was given. This offered an excellent opportunity for comparison of both drugs.

#### OBSERVATIONS

In 6 cases, following the amyl nitrite inhalation, the soft, grade 1 systolic murmur disappeared, and in four the murmur became louder. It was strange that 5 of the same 6 developed a grade 2 murmur after the epinephrine. Of the 4 in whom the murmur became intensified by the amyl nitrite, in 3 after the epinephrine the murmur completely disappeared, and in only one did the murmur remain loud. In the 2 organic cases the murmur of one became louder at the base after the amyl nitrite and softer after the epinephrine suggesting the likelihood of this case really being in the functional group (Table III).

Following the amyl nitrite, the pulses were accelerated up to 200 beats per minute and were rather thready. The systolic, as well as diastolic, blood pressures abruptly fell in all but one case to as much as 40 mm. of mercury (Chart 2 and Table III).

Following the epinephrine injections, in 14 patients the grade 1 murmurs either disappeared or retained their grade 1 quality. In 23 cases there was a distinct change in the intensity of the murmurs; 18 being placed in grade 2, and 5 in grade 3. In other words, by means of the epinephrine test we have decided that 62.1 per cent of a group of children with functional heart murmurs most likely have early cases of organic heart disease and should be observed accordingly. Of those in whom the murmur became intensified, 5 children presented a very loud grade 3 murmur along the left sternal border at the third and fourth

Table II 52 Cases With Observations Before and After the Epinephine Test

provosts	AFTER TEST	(1)	Class in	Class E		M. I.		Class E		M. T.		Class E		Cong. Pat.	I. V. S.	M. I.		Cong.	P. I. V. S.	M. I.		Class E		M. I.		Class E	
мевжив	APTER		Ry +	+	Ster.	+ +	Apex	+	Ster.	+	$\Lambda pex$	+	Base	+ + +	Ster.	++	Apex	+++				+	Base	++	Apex	+	Base
MUR	BEFORE		+ +	++	Ster.	+	Apex	+	Stor.	+	Ster.	+	Base	+	Ster.	+	Ster.	+	Base	+	Ster.	+	Ster.	+	Ster.	+	Ster.
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TABLE II-CONT'D

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108/60	112/60	110/60	130/80	07/40	130/70	08/20	09/06	09/96	92/60	110/70	120/80	108/60	120/80
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TABLE II-CONT'D

			5	MICAL	EPINEPIIRINE		PULSE	BLOOD PRESSURE	USSURE	MUI	MURMUR	DIAGNOSIS
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T.C. 9 M Class E 8	M Class E	Class E	 E4	8		80	88	104/60	120/80	. +	4 + +	M. IM. S.
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L.M. 11 F M.I. or 8	F M. I. or	M. I. or		ø		110	98	110/80	140/60	Ster.	- + + + +	Cong.
Cong.	Cong.	Cong.	cong.	_	_					Ster.	Ster.	P. I. V. S.

TABLE II-CONT'D

; ; ; ;	ij.	Class E	M. I.	M. I.	M. 1.	M. I.	M. I.	M. I.	M. I.	ox M. S.		M. I.	M. I.	M. I.	
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118/80	112/88	112/66	114/58	130/68	110/60	100/38	96/40	120/70	110/68			120/70	110/30	120/86	
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TABLE III
Effect of Amyl Nitrite and Epinephrine on the Murmur, Pulse, and Blood Pressure of a Group of Twelve Children

MURMUR			PULSE			BLOOD PRESSURE			
CASE	BEFORE AMYL EPI-	AFTER EPI- NEPH.	BEFORE TESTS	AFTER AMYL NITRITE	AFTER EPI- NEPH,	BEFORE TESTS	AFTER AMYL NITRITE	AFTER EPI- NEPH.	
	}	MILMIL	YELE.		2111111	VELU.	S. D.	S. D.	S. D.
1	+	_	++	80	160	92	112/50	100/40	140/58
2	+	-	++	88	164	96	120/70	104/58	140/38
3	+	+++	-	80	160	92	116/80	100/60	124/80
4	+	++	-	76	140	80	100/80	90/60	86/50
5	+	++	-	S4	100	78	90/44	70/30	110/60
6	+	) -	<b>+</b> +	104	144	98	102/84	76/44	108/52
7	+	-	++	96	180	120	120/80	112/30	150/70
s	+	-	++	SO	200	88	104/76	94/70	120/80
Ð	+	-	+	SS	160	92	120/76	90/62	124/84
10	+	+++	++	120	160	110	112/60	100/50	120/80
11	+	++	+	92	140	96	100/40	86/40	112/50
12	++	+	++	96	160	108	112/44	82/38	120/60

Key: +, grade 1 murmur, Class E, faint or soft.

interspaces. In our opinion the location and intensity of these murmurs justified a probable diagnosis of congenital heart defect, most likely due to a small septal lesion. In 16 cases a fairly loud systolic murmur appeared, with maximum intensity at the apex, transmitted to the axilla. These were considered cases of organic mitral insufficiency. Another child developed a very definite systolic and diastolic murmur near the apex, suggesting the probability of concomitant mitral stenosis. In one child with a history unknown, after the epinephrine, a loud diastolic murmur appeared at both the second right and third left interspaces. In this case a pistol-shot murmur was present in the groin, and the blood pressure changed from a normal of 120 systolic and 70 dias-

TABLE IV

GROUPS OF CHILDREN RECEIVING THE EPINEPHRINE TEST, WITH DIAGNOSIS BEFORE AND AFTER THE TEST

AFTER EPINEPHRINE

Before epinephrine, 37 cases Class E, func- tional murmurs	14 cases: same diagnosis, Class E 16 cases: organic mitral insufficiency 5 cases: congenital heart defect 1 case: mitral insufficiency and stenosis 1 case: aortic insufficiency
Before epinephrine, 15 cases organic mitral insufficiency	11 cases: same diagnosis, mitral insufficiency 1 case: congenital defect 1 case: nortic insufficiency 1 case: Class E 1 case: Class E and F

<sup>++,</sup> grade 2 murmur, moderately loud,

<sup>+++,</sup> grade 3 murmur, very loud.
-, no murmur.

tolic to a systolic of 140 and diastolic of 38. All these findings left no doubt in our mind that the child under consideration suffered from an organically incompetent aorta.

Of the 22 under ten years of age, there were 6 in whom the epinephrine diagnosis remained the same, while in 16 the diagnosis was changed to organic heart disease. Of the 15 children ten years old and over, 9 remained the same, and in 6 the diagnosis was changed. So evidently there appears to be a greater discrepancy in the cardiac diagnosis of younger children (Table IV).

The pulse rates before the epinephrine averaged 90.4 beats per minute; the slowest being 64 and the fastest being 120 beats per minute.

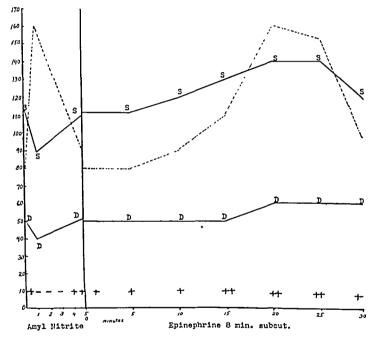


Chart 2.—C. W., female, aged twelve years, negative history. At rest a soft systolic murmur is heard along the sternum. After amyl nitrite no murmur is heard. After epinephrine a loud systolic murmur is heard at the apex and is transmitted to the axilla. Impression: Mitral insufficiency.

Pulse is indicated by the broken line; S, systolic blood pressure; D, diastolic blood pressure. Murmurs, -, none; +, grade 1; ++, grade 2; +++, grade 3.

Following the epinephrine the maximum rise was up to 160, while the lowest rate was 72 beats per minute. The average rate twenty minutes after the epinephrine was 95.3 beats per minute.

# DISCUSSION AND CONCLUSIONS

None of the cases tested presented any unusual difficulties. With a sensible introductory explanation of the test about to be performed, the children offered their complete cooperation. The amyl nitrite test was shown to be of absolutely no use for accentuating and differentiat-

ing precordial murmurs. In fact, in the majority of organic cases the murmur disappeared with amyl nitrite only to return and become accentuated following the epinephrine. This rather agrees with the findings of Kahler and is contrary to the opinion of Morison. Our explanation for these phenomena appears rather logical. Evidently the amyl nitrite merely serves to accelerate the pulse but at the same time decreases the force of the cardiac contraction, with a consequent disappearance of mild organic murmurs. The epinephrine, on the other hand, as shown by Hume, 15 Koppanyi, 16 Brodie and Cullis, 17 Wiggers, 18 Lewis and Hewlett,10 exaggerates the force of the cardiac contraction with a consequent increase of eddies and a resultant intensification of murmurs which are due to an early organic valvular defect. Because of the dilatatory effect of amyl nitrite on the blood vessels, it is quite likely to be the reason for the appearance of functional murmurs after its use. The epinephrine test, on the other hand, has proved to be of inestimable value in determining the probable early cases of valvular heart disease: 47.8 per cent of an original group of Class E cases so tested five years ago are today classified clinically as organic heart disease. The epinephrine test also shows its usefulness in accentuating the murmurs of the truly organic case in which the diagnosis must be deferred because of an uncertainty in the timing and in locating the point of maximum intensity of the murmur in question. In these cases the murmur becomes so intensified and localized as to make the diagnosis most certain.

We offer the epinephrine test for heart murmurs in children not as a panacea for the absolute differentiation of organic heart disease from the functional, but rather, as Dwan<sup>20</sup> says, "As a practical office method of hearing the murmurs more clearly should they be present." We wish to assert ourselves now, just as we have done in the past, on the question of the significance of the murmur. It is our opinion that a great percentage of the soft murmurs are significant and that the moderate and loud murmurs are always significant. We agree with others in declaring that the murmur per se is of no importance in determining the functional capacity of the heart in question. However, we urge that it is most important to recognize the presence of an organic murmur because it usually signifies the presence of an infectious process, either latent or active, most likely rheumatic in origin, and which we all know has a most vicious tendency to recur. If we know that the ease at hand is organic, we will necessarily be alert for any rheumatic manifestations. Only in this manner can we ever hope to conquer a most intractable condition. It is our concluding opinion that it is still preferable to err on the side of caution rather than neglect, acknowledging, however, that the psychic factors of the patient must be considered. used in order to prevent the additional burden of a mental hazard to an acquired organic physical defect. It is interesting to note here that Osler once said. "If an individual discovered early in life that he was suffering from a chronic disease, the probability was that he would not

die of that particular disease, he would deliberately take care of himself in respect to the handicap, so as not to allow that disease to gain headway; some disease he did not consider might readily overwhelm him." With our present-day method of handling and treating the ambulatory cardiac patient the dread of informing the patient of his affliction is practically nil. The functional capacity and curtailment of activities of the child depend, of course, on the cardiac response and not upon the presence of murmurs.

#### SUMMARY

The value of the subcutaneous injection of epinephrine 1:1,000 as a means of accentuating and differentiating the so-called functional cardiac murmur from the organic is discussed; a five-year clinical follow-up in a group of 32 children previously receiving this test being the basis. A new group of 37 children were given a similar test, using amyl nitrite in 12 for comparative effects. The epinephrine test is found most useful for intensifying the murmurs of the early cases of probable valvular heart disease and also in accentuating the murmurs of the definite organic valvular lesions. The similar use of amyl nitrite as recommended by others is found entirely wanting. Due to the fact that the authors find so large a percentage of children considered as having a functional heart condition, within a period of five years presenting the clinical signs of a recognizable organic cardiac lesion, they strongly urge the physician to be cognizant of the threatening importance of the cardiac murmur, even without the expected concomitant signs and symptoms of organic valvular heart disease.

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#### TRENDS IN CHILD PSYCHIATRY

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#### INTRODUCTION

CHILD psychiatry has developed in the last fifteen years from a study of delinquent children into a field concerning itself with the analysis and treatment of such behavior anomalies as develop not only in problem children, but in almost all children. It has broadened its base by the accumulation of added knowledge of normal mental and emotional development. It seeks to introduce mental hygiene concepts as an integral part of child care and education.

A factor important in shaping any particular clinic in which psychiatry for children is practiced is the relation that the clinic has to its community. Whether it be an independent unit, or a close associate of some social agency, or a function of a psychiatric department, this will influence not only its fundamental attitude, but also its whole point of departure, its personnel, its clientele. Classified roughly from this point of view, there are three main types of clinics functioning:

- 1. City-supported Child Guidance Clinics.
- 2. Psychiatric organizations serving social groups.
  - a. Those working in relation to hospitals or as an integral part of pediatric clinics.
  - b. Those working in conjunction with social-medical agencies.
- 3. Child psychiatric organizations in medical schools which are either within the pediatric department or affiliated with the psychiatric department. The tendency to teach the student child psychiatry and pediatrics simultaneously has increased in the last five years.

For purposes of a report it is convenient to group the organizations into two main types, namely "guidance clinics," which include the independent units, as contrasted with what we shall call the "psychiatric services," meaning those units which are connected with hospital, medical school, or social agency.

#### CLINICAL MATERIAL

Source of Cases.—In guidance clinics there is a tendency for the percentage of juvenile court cases to be diminished in favor of cases referred by social agencies, schools, parents, and physicians. The last

From the Child Guidance Clinic of the Federation of Jewish Charities.

Read before the Pedlatric Section of the California Medical Association at the sixty-fifth annual session. Coronado, May 25-28, 1936.

category is small, since the attitude especially of the older members of the medical profession is still not fully cooperative with the child guidance movement as such.

The psychiatric services affiliated with medical institutions obtain their material partly from the above mentioned sources, and, in addition, cases referred from the pediatric departments. The interest of the medical profession for cooperation is obviously better stimulated by this type of service on account of closer contact.

Selection of Cases.—In nearly all organizations the demand upon them is greater than can be filled. In guidance clinics a proper selection of cases is made through a committee of staff members who review the applications. In psychiatric services in connection with hospitals or social agencies, the physician determines after the first examination the degree of service appropriate for the specific case.

Age Groups.—Child guidance clinics have a large percentage of children in the teen age with school failures, in contact with juvenile courts, and with problems of adolescence. The psychiatric services on the other hand show a preponderance of children of preschool or first grades. This is due to the fact that pediatric departments become aware of early symptoms of abnormal behavior through their well baby or preschool clinics. The contact of such services with younger children seems to be of decided advantage since it places the accent on prevention through early discovery of behavior anomalies.

#### STAFF

In child guidance clinics the basic team for the examination of full service cases consists of pediatrician or physician, psychiatrist, psychologist, and social worker. The psychiatrist may also make the physical examination, or there is a division so that the medical examiner takes over the psychiatric attention of the preschool group.

In psychiatric services the pediatrician or psychiatrist plays the main rôle. Then psychologists or social workers are called upon either routinely or only in those cases in which their services are appropriate.

When the psychiatric service functions in connection with a social agency, the social worker is the central figure. She directs the case to a physician in clinic, hospital, or private office and either consults with the psychiatrist in the absence of the patient or brings the patient to the psychiatrist's office. The psychologist is not routinely called.

#### FORMS OF SERVICE

With the Chicago Institute as an example of the services offered by guidance clinics, the following forms of service may be distinguished:

1. Full clinic service includes study by full social history, a complete physical examination, psychologic tests, and psychiatric interview, and discussion by full staff meeting.

- 2. Special service is for less complex cases (mainly of mental deficiency or the question of it, advice regarding fitness for adoption, advice regarding exclusion from school or regarding commitment). A brief history covers pertinent topics. Physical examination is not done unless previously omitted or incomplete. Psychiatric interview is held with parent and child. Discussion in staff meeting follows.
- 3. Summary service is for urgent cases, for such cases as do not need a long-drawn-out work-up, or for patients who respond better to a more informal approach. The examinations to be given each of these patients are decided upon in the application committee meeting. Any additional necessary work-up is arranged by the examining physician. Ordinarily these cases are not discussed in the full staff meeting but informally among the various examiners.
- 4. Routine service is given to cases which are generally not urgent, especially those in which improvement through treatment seems dubious. Brief social histories are taken, and one or two examinations, perhaps psychologic and psychiatric, are made. Ordinarily there is only informal discussion among the various examiners. Wherever necessary, cases are transferred from summary or routine service to full clinic service.
- 5. Cooperative service: The policy of child guidance clinics varies in the problem of cooperative service. For instance, the Institute of Juvenile Research prefers its own social worker to make a case study and to attend to the follow-up treatment. On the other hand, the child guidance clinic in Cleveland has a considerable percentage of cooperative cases. There the responsibility for case work and follow-up treatment is given to the social worker of the social agency which referred the case in question to the clinic.

The services offered by psychiatric services may be discussed by taking the Cornell Psycho-Pediatric Clinic as an example. Here are found the following:

- 1. Consultation service, in which the psychiatrist examines the patient in the hospital or clinic and advises the pediatrician concerning diagnosis and treatment. The pediatrician retains full management. This group represents children in whom behavior problems or minor functional complaints are superimposed on organic conditions.
- 2. Cooperative service: The case is referred to the psychiatrist for examination. A conference between pediatrician and psychiatrist follows. The treatment of child and parent is undertaken under collaboration of pediatrician and psychiatrist. In this group are patients mostly with problems on the habit level, who require reeducation for themselves or their parents over a certain length of time.
- 3. Paedo-psychiatric clinic service: Patients are referred from pediatrician to psychiatrist for examination and treatment. This is done with the group of children having personality problems on a deeper level and requiring expert care.

Child Psychiatric Hospitals.—All types of organizations mentioned so far deal with out-patients. A small number of institutions admit patients into their walls for thorough studies. An example is the Child Guidance Home in Cincinnati. It is operated jointly by the Jewish Hospital and the United Jewish Social Agencies. The child is sent first to the pediatric department of the Jewish Hospital for a complete examination. If referred to the Guidance Home, the child takes his place in a family of fifteen. "In addition to the regular household tasks, that a child is normally required to do, manual training and extra curricular school work are given. During this period of observation, varying from two weeks to two months, the child attends the neighborhood public school where he is placed in a grade according to his mental capacity. The principal and teachers are informed regarding the nature of the child's problems, and their aid and cooperation are enlisted. tion to the regular schooling, a teacher visits the Guidance Home regularly to coach the children and to give them any special instructions that may be needed. Psychiatric examinations and psychologic tests are also carried out at the Guidance Home." The child's social reactions both at school and at the Home are thus studied. Before a child is discharged, a conference of the Home staff with workers of interested agencies or parents is held in most of the cases. A careful follow-up with reexamination of the children in the Home follows. This type of work makes possible thorough study away from the influences of the previous environment and has the advantage or disadvantage of such a procedure.

#### METHODS OF APPROACH

The method of approach to any given case is influenced by a variety of factors.

- 1. A first point is the route by which a child reaches the clinic. This may be through social agencies, through medical agencies, or through private individuals, parents, or physicians.
- 2. The expected work to be done may be diagnosis or diagnosis plus treatment.
- 3. Clinics may be organized independently or in relation to other agencies, as outlined above.
- 4. The emphasis of the work may or may not be on education of community, social agencies, school principals, members of various professions, students of medical schools, teachers' colleges, schools of social work, or lay groups, etc.
- 5. Child psychiatric institutions are still in the stage of transition. Their work started as a help to the juvenile courts, soon became necessary to social agencies and schools, and has recently become associated with medical institutions. In the course of growth, many technics have been developed, which are still not completely standardized.

There is no wonder that, with so many factors working, methods of approach to the case are varied. An attempt to classify these methods is difficult, but certain working procedures seem to represent real differences in trend, even though they have some features in common.

The typical child guidance clinic approach may be demonstrated by a description of the procedure in the Institute for Juvenile Research in Chicago. Here the initial history is taken by the social worker with special reference to human interrelationships and attitudes. This is followed by psychologic, medical, and psychiatric examination and staff meeting.

In psychiatric services, of which the Johns Hopkins Clinic may be described as an example, the examining physician takes the complete history in the following order: complaint; onset and evolution of difficulties; family and social history, including interpersonal relations in the home, family history of serious illness, character traits, peculiar social and economic features, home conditions, home economics, family recreations, estimation of personalities; personal history of the patient, including developmental data, history of habit formation and home management, personality traits; distribution of work, recreation, rest over twenty-four hours, school record; physical status; mental status, including behavior during examination and intelligence test, complaint as formulated by the child, attitudes toward family members, playmates; diagnostic reformulation stating summary of assets and liabilities of constitution, physique, intellect, emotion, and environment. of a psychologist and a social worker is employed only for the investigation of special problems.

The difference of these two methods of approach is evident. In the first method several specialists in their respective fields pool their findings and decide about procedure in group discussion. This set-up obviously can cope with many more cases than can the second method, by which only one problem can be attacked in one-half day's work. The second method has the advantage of collecting all data through one person who thereby gains a very intimate contact with mother and child. But he may get only secondhand information about the social aspects. The psychologic examination is limited.

A third method of approach is practiced only in the Child Guidance Clinic of Philadelphia, where no organized history is taken. Instead, the psychiatrist starts his treatment with the child in the first meeting; the social worker begins similarly with the mother. Facts pertaining to the history come out unsolicited. Medical examinations or psychologic tests are not routinely performed.

It is obvious that this time-consuming method cannot be applied in institutions with a heavy case load. The method presupposes also that children with medical problems and feebleminded children, as well as children with reading disabilities, are eliminated beforehand.

#### METHODS OF TREATMENT

A pluralistic approach to the study of behavior problems in childhood implies a similarly pluralistic attack in treatment:

- 1. Medical treatment of all important organic factors involved.
- 2. Environmental manipulation, i.e., family, home, school, recreation.
- 3. Psychotherapy for child and relatives.

All three methods are used by all types of child psychiatric organizations. But one or the other method may be more or less available, or more or less prominent in the therapeutic attitudes of the staff. In general, it may be said that child guidance clinics with their close relationship to social agencies and with their heavy case load favor the second method with only limited consideration of the first and the third.

Psychiatric services connected with the hospitals may favor the medical aspects of treatment in combination with individual psychotherapy and environmental manipulation.

Some institutions (Child Guidance Home in Cincinnati, Child Guidance Clinic in Cleveland) are especially active in endocrine therapy of behavior disorders.

A few words on psychotherapy may be appropriate. The choice of the psychotherapeutic technic depends upon many different factors, mainly the personality and treatment philosophy of the therapist, the degree of the emotional disturbance of patient and mother, the time available, the qualifications of the social worker.

There is no uniform psychiatric philosophy existent. Psychobiology, as exemplified by Adolf Meyer's teachings, Freud's, Adler's, and Rank's teachings are the bases of the four main schools of thought. The personal choice of psychiatrist and psychiatric social worker, or a more or less "official" clinic policy determines the handling of the patient.

This division of opinion is not so noticeable in the treatment of behavior problems, which are supposedly superficial disturbances of personality. In complexes or conflicts of less than neurotic level the methods of suggestion (reassurance or encouragement) and of eatharsis (talking out) are employed everywhere. Nearly all psychopediatric institutions use the psychotherapeutic aids of occupational and recreational programs and training in basic habits of regulated living on the didactic level of treatment.

But in problems involving deep personality disturbances, where psychoanalytic therapy of some kind is essential, many controversial issues appear, of which the following are examples:

Should the mother be treated? The stress within the child is frequently caused by an emotional upset of the mother. Should mother or child or both be treated by psychoanalytic methods?

How should treatment proceed? Should mother and child be treated by the same therapist? In many child guidance clinics and psycho-

pediatric clinics this is done, but in the child guidance clinic of Philadelphia, for instance, the psychiatrist treats the child and the social worker treats the mother.

What is the lower age level for analytic treatment? Many clinics put the lower age level of direct treatment at seven to ten years. But in several institutions children in the preschool age are analyzed with play technics which give opportunity to dramatize and release emotional conflicts.

#### EDUCATIONAL ACTIVITIES

Child guidance clinics serve as training centers for psychiatrists and social workers. Students of schools for social work spend there a part of the period allotted for field training or work as postgraduates on special fellowships. Psychiatrists stay for one or two years as fellows or visit the elinics over periods of from three to six months. Staff members serve as teachers in various schools of social work, education, medicine, and nursing.

In addition, lectures are given to parent-teacher organizations, social agencies, school-teachers, and high school students.

Staff members serve frequently on committees of welfare organizations.

In child psychiatric clinics the teaching contacts are mostly with the medical and nursing profession, especially with medical students, house officers, and attending hospital staff.

In child psychiatric clinics connected with social agencies, the main teaching activity is devoted to social workers.

These manifold educational activities show clearly the far-reaching influence of child psychiatric organizations upon dissemination of mental hygiene concepts into the whole community.

#### CLINICAL CHILD PSYCHIATRY IN RELATION TO PEDIATRICS

The pediatrician meets in his daily work a considerable number of children who show physical manifestations of emotional disturbances. His close contact with the family and its setting gives him the opportunity to recognize them early and to influence the causative factors in the interplay of personality and environment. The pediatrician has now the knowledge at hand to influence the routine care of the child from birth to maturity in the terms of mental health. Therefore, he should be able to devote his attention to the emotional as well as to the physical problems for prevention and treatment.

This attitude will enable the pediatrician to cope with the majority of the everyday psychiatric problems of childhood. A relatively small number of children with deeper emotional disturbances have to be turned over to the psychiatrist for diagnosis and treatment.

The tendency of bringing the psychiatric viewpoint into pediatrics instead of turning pediatric-psychiatric problems, in general, into the psychiatric departments has brought the child psychiatrist into the pediatric department for close cooperation. This is a reason why child guidance clinics and child psychiatric services have been established within the children's departments of medical schools and general hospitals in recent years.

#### SUMMARY

- 1. Organization and activity of child guidance clinics and pediatric-psychiatric services have been reviewed.
- 2. The accent in child psychiatry has shifted, as it has in medicine generally, from treatment to prevention.
- 3. An important phase in the recent development of child psychiatry is the organization of child psychiatric services within pediatric departments. Here behavior problems are handled, together with all the other problems of children.
- 4. The pediatrician should be the main factor in the field of prevention and treatment of behavior problems in childhood.

POST AND SCOTT STREETS

## American Academy of Pediatrics

## Proceedings

# SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, Mo., MAY 11 AND 12, 1936

Round Table Discussion on Passive Prophylaxis Against Infection in Childhood

Chairman: John A. Toomey, M.D., Cleveland, Ohio. Assistants: Archibald L. Hovne, M.D., Chicago, Ill.

Sidney D. Kramer, M.D., Brooklyn, N. Y. Edgar E. Martmer, M.D., Detroit, Mich. Edward B. Shaw, M.D., San Francisco, Calif.

Passive Prophylaxis Against Pertussis and Chickenpox E. B. Shaw, M.D.

The success which has attended the use of convalescent serum and similar agents for protection against measles and for modification of this disease and the accurate information which has accumulated regaining this procedure naturally suggest that similar measureas might prove effective against many other of the acute infections, especially those due to viruses. The use of convalescent serum for passive protection against chickenpox and whooping cough has been applied to some extent and reported with varying degrees of success by different observers. The prophylactic use of human convalescent serum is essentially devoid of unpleasant reactions which accompany the administration of horse serum, and the duration of immunity thus conferred by homologous serum is more prolonged than that conferred by heterologous serum in the diseases in which immunity may thereby be transferred. The use of human serum, however, involves the clinician with somewhat greater responsibility regarding its collection and storage and in safeguarding against the possibility of thus transferring to the patient some other communicable disease than is the case with commercially prepared horse serum.

There is no practical method by which human convalescent serum can be assayed for its content of immune bodies. In contrast to commercially prepared serum, convalescent serum is not the result of hyperimmunization and is usually not extremely potent. Obviously the immune properties of convalescent serum are subject to great variation in different patients, and the protective value thereby differs greatly in various infectious diseases. The precise value of convalescent serum as a prophylactic can be determined only by clinical experimentation with a particular disease and by the results of carefully controlled and studious observation of patients; it cannot possibly be deduced by a simple analogy to the protective action of measles convalescent serum.

Kereszturi, Hauptman, and Parki report the use of convalescent serum in hospital practice for protection against several of the common contagious diseases of

children with varying success. They express the very cogent opinion that, unless control patients are observed simultaneously with treated patients, one cannot determine the value of convalescent serum. It is a matter of extreme difficulty to carry out clinical experiments under conditions which simulate to any degree the accuracy of a carefully controlled experiment with laboratory animals, but in order to provide information regarding the practicability of prophylaxis by means of convalescent serum against any specific infection it is essential that the conditions of laboratory experiments be reproduced as closely as possible.

It is quite certain, however, that the patients comprising a group to be studied represent only one of several variables which must be controlled. The susceptibility of the patient to infection is modified by age; in infancy susceptibility is high in some infections and is very low in others; early childhood represents a stage of increased susceptibility to most infections; advancing years usually reduce susceptibility through spontaneous immunization from exposure, subclinical infection, and increase in nonspecific resistance. Increase in the size of the patient may occasion the necessity for increasing bulk of the infecting dosage to which the patient must be exposed and undoubtedly increases the amount of serum necessary for his protection. In an experimental series there are certain to be differences in the intimacy of exposure to infection; minute amounts of infective material acquired through casual exposure may result in much milder attacks of a disease than are occasioned by massive exposure and consequent acquisition of large amounts of the infecting organism. Massive exposure to an infection may even occasion disease in the presence of partial immunity, as illustrated by the relative frequency with which mothers acquire second attacks of whooping cough from infected children. The susceptibility of the patient is influenced not only by his age, size, and intimacy of exposure but by factors which may affect his general well-being, such as antecedent or accompanying infection, injury, climate, exposure, and other physical and physiologic agencies. It is impossible for any group used as a clinical study to be subjected to the same degree of control as a laboratory experiment. A mathematically valid study of such a series would necessitate the impossible expedient of inoculating healthy individuals with a similar dose of infected material (as was done in one experiment regarding the etiology of whooping cough).2

Another variable factor affecting the efficacy of prophylaxis is the time interval clapsing after exposure before the administration of convalescent serum. The influence of this factor has been accurately studied with regard to measles, but there is evidence that it is important in other infections as well.

The potency of the convalescent serum used is of great significance to the validity of a clinical study. Human serum lacks the hyperimmune properties of the serum of immunized horses, but there are also quantitative differences in serum immunity production in different individuals just as there are in different horses. The interval after attack at which serum is collected influences its potency; a maximum is reached some time after defervescence, from which there is a variable rapidity of decline in different individuals and in different infections. The persistence of a considerable degree of potency which may be present long after an attack of measles cannot be confidently anticipated in other infections. The intensity of infection seems likely to influence to an unpredictable extent the amount and persistence of immune substances. It would seem desirable that the dosage of convalescent serum administered to the patient be chosen with some regard to its potency and with respect to the size of the patient, the degree of exposure, etc.

To say what has been accomplished with a single serum in the protection of an individual patient cannot possibly comply with these controlled conditions. In order to pursue an acceptable study of this problem, it is necessary to study a sufficiently large group of cases, to provide adequate controls, to administer serum at a definite period after exposure, to use pooled serum obtained at a definite and

preferably early period of convalescence, and to administer to each patient an amount of serum sufficient to produce a presumably maximum effect. Except for studies on measles and some few other notable exceptions, clinical studies regarding the prophylaxis of the common infections of childhood have been pursued with little regard to these criteria.

Whooping Cough.-The literature of whooping cough prophylaxis by means of convalescent serum has been well reviewed by Bradford3 and by Kereszturi and her associates.1 The spontaneous variability of whooping cough is so great that, even if factors of exposure-dosage, time, and serum potency-were kept constant, a large number of case observations would be required for an adequate field test of effectiveness. In reported observations there has been so little constancy in these factors that it is doubtful if any one series or even the aggregate of all reports present really valid evidence. Kereszturi controlled her series carefully, but had no occurrence of the disease in either treated patients or untreated controls. Bradford conducted critical studies of a comparatively small group using whole blood of adults who had whooping cough in childhood as well as serum from recent convalescents. Bradford's series is too small for conclusion, but he presents a clinical opinion which summarizes his own experience and coincides with the majority of the most careful reports. He believes that convalescent serum, and probably the blood of adults who have had whooping cough in childhood, contains active principles capable of modifying the course of the disease if applied early in the incubation period before the onset of even the early catarrhal stage of infection. It will be difficult to determine the final truth of this opinion, but there is sufficient need in many cases for the prevention of severe whooping cough that it should be worth while to collect serum for use under conditions of intimate exposure in patients in which occurrence of the disease would be especially undesirable. There is no method of biologic assay of serum, but, if stores of serum were collected early in convalescence and applied to cases early after exposure, it should be relatively easy to determine if anything can thus be accomplished and having accurately established this fundamental point comparative studies could be made regarding the value of blood obtained from immune adults, the utility of applying serum later in the disease, and the effect of increasing dosage at various

Chickenpox.—Chickenpox is in general a very mild infection, and prophylaxis against it is seldom desirable. An exception to this general statement is found in institutions in which it would often be desirable to protect because of one's medical responsibility to the patients and because of the undesirability of prolonged quarantine of a ward. Aseptic nursing in a children's ward often protects against the simultaneous development of secondary cases of chickenpox among all of the inmates, but the slightest error in technic often permits many generations of secondary attacks. Chickenpox is, furthermore, sometimes peculiarly severe in the convalescence of other infections, and for this reason it would sometimes be desirable to confer passive protection at such a time if this were possible.

Gordon and Mender4 and Kereszturi and her associates1 have reviewed the literature of chickenpox prophylaxis, which is not extensive, most thoroughly. Kereszturi was unable to draw any conclusions from her experience with the disease. Gordon reports the study of a series of ward exposures in which prophylaxis was attempted and in which many of the experimental variables were adequately controlled. Gordon did not directly control his patients, but there is some control effect in the comparison of different groups in which different procedures were tried. He presents several conclusions which are well supported by his experience and by the reports of other observers. These may be summarized as follows: The blood of convalescents contains protective immune substances against the virus of chickenpox. Serum immunity production is apparently poor in infants and young children, is better in older children and adults. Serum immunity is high immediately following attack

but reaches a low point from five to ten months after an attack; accordingly blood serum for prophylaxis should be withdrawn within one to two months of an attack. Protection is usually secured in children by the administration of 10 c.c. of blood serum given within twenty-four hours and not later than the third day following Although immunity is usually conferred, approximately 10 per cent of cases escape protection and develop the disease in unmodified forms. Passive immunity is brief but apparently longer than that conferred by heterologous serum; twelve patients reexposed to secondary cases resulted in two clinical cases, one boy was apparently protected against three exposures within an interval of forty-seven days.

None of the published observations answers the question of what can be accomplished with larger doses of convalescent serum later in exposure, or of what can be accomplished with larger doses of adult serum, or if it is possible to obtain complete protection in a series by a sufficiently large dose of serum.

A single observation of our own illustrates the lack of correlation between chickenpox and measles regarding the protective value of large amounts of adult blood. A ten-year-old boy suffering from scarlet fever received at intervals transfusions of 250, 300, and 300 c.c. of blood from two donors. Within less than two weeks of the last transfusion he developed chickenpox from ward exposure. These transfusions would almost unfailingly have protected him against measles but failed perceptibly to modify the course of his chickenpox.

This disease is ordinarily mild; protection by any known method is far from absolute; there is accordingly infrequent necessity of using this method for prophylaxis. A considerable minority of cases fails to be protected, and those protected against the original exposure may become susceptible to reexposure to secondary cases. It would seem not to be at all obligatory to attempt the protection of children's wards during outbreaks.

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#### DISCUSSION

DR. KRAMER.—Are there any methods of titration for pertussis immune scrum?

DR. SHAW.—There is no absolute method. One measures the effect by clinical trial.

CHAIRMAN TOOMEY .- Freshly isolated phase I organisms when injected into rabbits produce a serum with an agglutinin titer value as high as 1:40,000. Yet such serum gives no protection to guinea pigs, for when protected and nonprotected animals are injected with Type I organisms the protected animals die sooner than do the unprotected controls.

DR. SHAW .-- I would conclude by stating that convalescent pertussis serum may be of some value in prophylaxis, although this has not been proved and state also that there is no evidence that convalescent serum is of any value in chickenpox. In fact, in my opinion it is a question whether or not it is a practicable procedure to even inject exposed susceptible children.

CHAIRMAN TOOMEY .- Dr. Shaw's remarks are timely. He points out the danger of drawing too many conclusions from isolated experiences. He stresses the need of controls and the fact that all diseases have a natural history of their own. Every clinician should read his remarks before talking about the beneficial results obtained from the use of any therapy.

Convalescent serum has not been very helpful in controlling the spread of chickenpox in our wards.

I thought that whooping cough convalescent serum might be of value in the treatment rather than in the prevention of whooping cough, but the evidence is questionable.

DR. HOYNE.—I question the value of chickenpox serum for prevention even when as high as 20 c.c. were given.

DR. M. G. PETERMAN (MILWAUKEE).—I have tried immunization with the vesicle fluid of chickenpox lesions and found it worthless.

DR. J. F. SANDER (LANSING, MICH.).—What about the danger of transmitting the disease when fluid from lesions is used?

CHAIRMAN TOOMEY.—One year chickenpox broke out, and in the entire contagious disease hospital we vaccinated 91 children (against chickenpox) with the contents of varicella vesicles, and in due course SS of the 91 children came down with the disease.

DR. M. L. BLATT (CHICAGO).—In an orphanage housing 250 children I have used normal human serum in those exposed to chickenpox, and 10 c.c. seemed to give protection for eight days; but, if a second case developed in the house, the disease would become epidemic. There were four cases of gonococcus vaginitis; convalescent serum was given and the children were protected for three months—though repeatedly exposed.

DR. SHAW.—Massive doses are required for prophylaxis; the longer the interval after exposure, the larger the dose required. I do not believe that varicella vesicle fluid (active immunization) is of any value, for, when I tried it, the children developed the disease anyway. In general, one could say a children's ward is a poor place to evaluate the worth of material. It can be done well only in private practice.

#### Convalescent Scarlet Fever Serum for Passive Immunization Archibald L. Hoyne, M.D.

The need for some satisfactory method of passive immunization against scarlet fever is apparent. This requirement is particularly evident when the scarlet fever patient remains in a home where there are susceptible children. Even when the original patient is removed to a hospital, there is no assurance that other members of the family may not be in the incubative stage of the disease as a result of exposure. In this connection, it is well to keep in mind that scarlet fever is not uncommon among adults.

In a published report we have cited several groups of multiple cases occurring in the families of children admitted with searlet fever at the Chicago Municipal Contagious Disease Hospital. From January, 1932, to July, 1934, there were 1,771 such multiple cases. This total represented 730 families in which scarlet fever was transmitted in the home by direct contact from a known source.

During the past few years, our hospital figures have indicated that there has been a progressive increase in the number of multiple cases of searlet fever. For example, in 1932 there were 488 multiple cases; in 1933 the number was 761; and for the first six months of 1934 the total reached 522. Had a reliable prophylactic been available when the first case of scarlet fever developed in each of the 730 families concerned, some lives, considerable money, and a great deal of time would have been saved. Furthermore, the inconveniences attending quarantine would have been avoided by those who were protected.

Convalescent searlet fever serum has been used for a number of years with the intention of conferring passive immunity. In some reports of its administration, the

value of its protective properties is not clearly proved. Since the question of susceptibility of the contacts was not always determined, failure to contract scarlet fever could not in every instance be attributed to serum injection. It is for this reason that both Degwitz' and Meader's results are somewhat uncertain. On the other hand, the Dicks and Gordon showed conclusively the protective qualities of convalescent scarlet fever serum. The latter reported 92 per cent protection in a group of Dick-positive student nurses who reported for duty in the Herman Kiefer Hospital. Each of the 112 nurses was given 15 c.c. of luman convalescent scarlet fever serum, intransuscularly, before entering the scarlet fever ward. Eight nurses contracted scarlet fever, but apparently the disease was modified. In fact, it was Gordon's belief that had it not been that these nurses were under close observation, a diagnosis of scarlet fever would have been missed.

We have reported on the inoculation of 862 home contacts in which 97.2 per cent did not develop scarlet fever. This series, like some of the others referred to, is vulnerable in respect to displaying the actual efficiency of the serum. Although none of the number gave a history of having had scarlet fever, susceptibility as indicated by the Dick test was not determined. There were, however, 83 Dick-positive hospital contacts who received convalescent scarlet fever serum. For these, protection was indicated in the 95 per cent who did not develop scarlet fever.

Human convalescent scarlet fever serum is a reliable prophylactic agent. If administered to a susceptible individual within twenty-four hours of exposure, it is almost certain to convey a passive immunity. If given at a later time, it is likely to modify if it does not prevent scarlet fever. Immunity when established by the injection of convalescent serum is not likely to endure more than ten days to two weeks. Therefore, if there is continued exposure or a second exposure after ten days, the dose should be repeated. Because it is a human serum, no unpleasant reactions need be anticipated when a second or third dose of convalescent scarlet fever serum is administered.

Usually 10 c.c. is sufficient for a prophylactic dose of convalescent scarlet fever serum, although a larger amount will do no harm. The serum should be warmed to body temperature. The outer muscles of the thigh offer a good site for injection. If the contents of the syringe are expelled slowly into the muscle, practically no pain will be felt.

In some of the larger cities serum centers are maintained. Detroit, Chicago, Cleveland, and Milwaukee are among the places which provide human convalescent serum to physicians who desire to use it.

At times it may be difficult or impossible for the physician to secure convalescent serum for the immediate needs of his patients. Under such conditions, he may, if the circumstances seem sufficiently urgent, resort to the use of whole blood. The supply may be obtained from one of the parents of his patient. Preferably, the parent should have a history of having had scarlet fever or of being Dick negative. If whole blood is used for the purpose of passive immunity, about 30 c.c. should be injected deep into the muscle.

The secondary case of scarlet fever in a family is frequently much more severe than the primary case. This is a fact well worth considering when contemplating the advisability of attempting passive immunization of contacts.

#### DISCUSSION

DR. C. A. EARLE (DES PLAINES, ILL.).—Does convalescent searlet fever serum influence the Dick test when given susceptible individuals?

DR. HOYNE,—Negative Dick tests have been seen after the use of convalescent scarlet fever serum, but unfortunately there was no knowledge of what the Dick tests were preceding these injections.

- DR. JOHN AULL (KANSAS CITY, Mo.) Does convalescent serum influence angina?
- DR. HOYNE.—In my opinion, there is a marked improvement in throat conditions.
- DR. J. V. GREENEBAUM (CINCINNATI).—How long does convalescent serum stay potent?
  - DR. HOYNE.-We find that it is still potent after a year in the ice box.
- DR. SHAW.—How would you compare the horse serum antitoxin or antiserum and human serum?
- DR. HOYNE.—Many object to the use of antitoxin as a therapeutic measure because of the reactions which follow its use. The new scarlet fever antitoxin of Lederle's gives but few reactions.
- DR. KRAMER.—Should there be reactions to human serum, they are mostly due to a passive transfer of an allergic principle.
- CHAIRMAN TOOMEY.—Human serum does not cause any immediate reactions, but I have seen maculopapular rashes come on from seven to fourteen days after its use. These rashes are fleeting in character, and appear like a mild erythema multiforme. There are no striking subjective or objective symptoms associated with it.
- DR. J. E. DYSON (DES MOINES, IOWA).—Is typing necessary when human serum is to be used intravenously?
- DR. HOYNE.—It is not absolutely necessary, but it may be advisable perhaps to type the serum against cells in cases in which intravenous injections are done. Gordon has shown a 92 per cent protection rate when convalescent serum was used prophylactically in nurses.
- DR. E. G. HORTON (COLUMBUS, OHIO).—When serum is given intravenously, is it undiluted?
  - DR. KRAMER.—Is the preservative a causative factor in these late reactions?
- DR. HOYNE.—The serum has been used undiluted "as is." I do not believe that preservative has much to do with reactions.
- DR. MARTMER.—It may be of interest to know that in some work we have done, we have been able to change a Dick-positive individual to Dick negative by the use of convalescent scrum. The reaction, however, is reversed in from nine to twenty-one days after the scrum is given.
- DR. ARTHUR F. ABT (CHICAGO).—If frequent Schick-testing creates immunity, is it not possible that frequent Dick-testing may produce immunity also?
- DR. KRAMER.—I agree with Dr. Abt that frequent Schick-testing reverses positive reactions.
- DR. SHAW.—We have never found evidence that frequent Schick-testing influenced the reaction.
- DR. M. K. WYLDER (ALBUQUERQUE, N. M.).—Is this new product of Lederle's safe?
- DR. HOYNE.—About 20 patients were injected with this new antitoxin without any reactions. The material is highly concentrated and purified. So far as I know, it is safe.

CHAIRMAN TOOMEY.—We also have injected 20 patients with the same material. Our previous reaction rate has been from 75 to 80 per cent with various scarlet fever antitoxins used. Since there was a 25 per cent reaction rate in our 20 cases with the new product, even though it is better, at least in our experience, it has not completely lost its possibility of reaction.

- DR. KRAMER.-Is the Dick test a measure of immunity or susceptibility?
- DR. HOYNE.—Of 800 nurses who were immunized at the Cook County Hospital, only one developed scarlet fever. It is perfectly possible to have scarlet fever without a rash and to have the complications of scarlet fever. These are passed as streptococcic sore throats. One may question the statement as to whether one merely desensitizes against the rash.
- DR. ABT.—Do you use convalescent serum in these cases of streptococcic sore throat?
  - DR. HOYNE.—Convalescent serum may be used; the patients have improved.
- DR. EARLE.—I have from 700 to 1,000 children in an institution, and I find that immunization is an invaluable procedure to check diphtheria and scarlet fever. Only two children who were Dick negative developed scarlet fever. Only two children likewise had such reactions that active immunization has had to be discontinued.
- DR. MARTMER.—Dr. Toomey, in your experience does scarlet fever follow previous mastoiditis?

CHAIRMAN TOOMEY.—Rarely. It is the other way around: Mastoiditis follows scarlet fever. The point in discussion is passive prophylaxis, but, since active immunization has been touched upon, I just wish to say in passing that I think that it has definite value. All nurses with sore throats are admitted to our wards, and there has been no increase of streptococcic sore throats in this group in the past ten years.

- DR. WYLDER.—Would you recommend active immunization for children of preschool age?
- DR. HOYNE.—That may be the best time, since theoretically these individuals are supposed to have lost their passive immunity and have become susceptible.
- DR. F. H. MAURER (Peoria, Ill.).—What is the relative permanency of active immunization?
- DR. HOYNE.—The evidence is not clear. Some claim seven years; most three years, at least. You cannot depend on passive prophylaxis after ten days.
- DR. O. E. BARBOUR (Peorla, Ill.).—It is my experience that the earlier you give scarlet fever toxin for active immunization, the less reaction you get. Would you give it before diphtheria toxoid?
- DR. EARLE.—The younger the child the less reaction you get after immunization. I give it as early as fourteen months.
- DR. G. H. FELLMAN (MILWAUKEE, WIS.).—Is it not a fact that the more severe cases of scarlet fever occur in those patients who have large tonsils and adenoids?
  - DR. HOYNE.—Yes.
  - DR. ABT.—What is the status of Veldee's detoxified antigen?
- DR. J. P. LEAKE (Washington, D. C.).—This is a formalized preparation. It does not give perfect immunity and also may give reactions. It is in the state of experiment.

- CHAIRMAN TOOMEY.—Bradford, of Rochester, has been experimenting with Ando's fraction of the scarlet fever toxin, but there is nothing definite to report at this time.
- DR. F. P. GENGENBACH (DENVER, COLO.).—Would it not be better to take the tonsils out in the preschool period? Would it be impracticable to increase the number of doses and thus cut down the reactions?
- DR. HOYNE.—It is always wise to have enlarged tonsils removed, and the preschool time is possibly as good as any. It is a question as to whether people would stand for an increased number of doses.
  - DR. KRAMER.—Has control series been observed in Chicago?
  - DR. L. M. EARLE (HOLLYWOOD, CALIF.) .- Do you collect fasting blood?
- DR. MARTMER.—Is there any danger when a second or third dose of convalescent serum is given? I thought that I had seen urticaria and serum reactions as a result.
- DR. A. D. BIGGS (CHICAGO).—What dose of serum did you use? I have had success with 20 c.c. amounts.
- DR. HOYNE.—A small amount of convalescent serum (human) given every ten days during intimate exposures will prevent the disease. I use 10 c.c., Gordon used 15 c.c., and Meader 7.5 c.c. I do not use antitoxin as a prophylactic.
- DR. BLATT.—Cross infection is a problem in any children's hospital. At Cook County Hospital, all patients admitted, whether medical or surgical, are treated as suspects and given 30 c.c. of whole blood. When a case of scarlet fever does happen to appear, all the children are Dick tested and have their throats cultured. All positive cases are given convalescent serum (human). As a result, Cook County Hospital infants' and children's wards have not closed for quarantine in over two years. In Chicago a serum center supplies convalescent serum. I believe that parent's blood has some value and is worth using when convalescent serum is not available.
- DR. C. A. EARLE.—Scarlet fever is not so contagious; often only one case develops in a family. If a case develops in one of my families, I make Dick tests on all members of the family. Those who are positive I actively immunize by giving them the five doses of Dick toxin. I feel that immunity begins at once.
  - DR. BLATT .- Have you (Dr. Earle) had any scarlet fever in these cases?
  - DR. C. A. EARLE .- I cannot recall any case-.
- DR. SHAW.—I feel that I would like to stress Dr. Hoyne's remarks about the return cases. I would like to ask Dr. Blatt if he would recommend the use of parent's blood in exposed cases without a test?
- DR. J. I. DURAND (SEATTLE, WASH.).—It would seem that one would have to think of the danger of syphilis when using blood for prophylactic purposes.
- DR. BLATT.—I have had only one accident as a result of blood injections, and this was due to the fact that there were in the hospital at the same time two children with the same name. I have never known malaria to be transmitted. I usually use the mother's blood.
- DR. HOYNE.—Control is the way to stop the spread of the disease; quarantine will not do it. Often the second case from the home is not the one from the hospital case—but really a new case.

CHAIRMAN TOOMEY.—I wonder how practical is Dr. Blatt's procedure of culturing the throat. Most throats have streptococci.

DR. BLATT.—At least 40 colonies must be on a plate, hence the evidence is relative. In short, the culture must be very positive as it were.

#### Passive Immunity Against Encephalitis, Mumps, and Erysipelas John A. Toomey, M.D.

Hess withdrew blood from patients who had had mumps within two years and injected from 6 c.c. to 8 c.c. and thought that he had protected susceptible children who were exposed. Regan injected from 2 c.c. to 4 c.c. of blood serum withdrawn from ten to twenty days after mumps started and felt that it protected if given before the seventh day after exposure. If given late in the incubation period, orchitis may be prevented. This is probably the most practical time for injection. Others have injected as high as from 10 c.c. to 20 c.c. of serum to protect and to prevent orchitis. Teissier, quoted by Shamberg and Kolmer, observed 23.29 per cent cases of orchitis in a series of 172 boys who had no serum and only 8.13 per cent in 172 boys who had the dose mentioned above. There seems to be some evidence that convalescent mumps serum may prevent orchitis if given after the onset of mumps and may actually prevent the disease in a susceptible child if given early enough after exposure. From 10 to 20 c.c. of serum should be given intramuscularly to be of value.

Erysipelas.—From 10 to 15 c.c. of concentrated erysipelas antitoxin has been recommended to be injected intramuscularly into exposed children. Since, in our hands at least, erysipelas antitoxin does not stop the spread of the natural disease when used therapeutically, since even an attack of the disease is apparently not followed by much immunity, and since patients actually seem more susceptible if they have been once attacked, it hardly seems logical to expect that serum would prevent the disease in others. Situations arise, however, as in surgical floors, where one or more cases may break out. It may be to the best interests of the physician to try to prevent any spread of the disease by the use of serum. At least, we have the consolation that, if it does no good, it will not do much harm since for some unknown reason it is not usually accompanied by the severe serum reactions seen when other antitoxins are used. There are no accurate data, and hence no definite conclusions can be drawn as to protection. I feel that, if exposed children wash their hands well with plain soap and water each time a patient is touched and if they refrain from scratching themselves, they will have nearly complete protection.

Encephalitis.—Convale-cent serum has been used in encephalitis as well as antiinfluenzal serum. The morbidity to this infection is low, and the chance for contraction minimal even to a per-on exposed. The evidence would not lead us to endorse the use of manufactured serums. Perhaps convalescent serum may prevent the infection from occurring in susceptible persons, but I know of no way of determining its efficacy.

We do not encourage its use in passive prophylaxis, although there may be some value in its use as a therapeutic measure.

#### DISCUSSION

DR. BARBOUR.—Would not early smallpox vaccination prevent postvaccinal encephalitis?

DR. LEAKE.—The number of cases of encephalitis that have occurred in the United States is negligible considering the number of individuals vaccinated. We have learned by experience that even this small number may be cut down practically to zero if the primary vaccination is given early, i.e., during the first six

months. It is better possibly to give smallpox vaccination first and then to follow it by diphtheria immunization. There is, as you know, evidence of nonspecific enhancement of immunity during the process of immunization.

DR. SHAW.—It is our experience that infants immunize poorly against diphtheria toxin.

DR. LEAKE.—Immunization against diphtheria would be better done at a later date, about one year.

DR. GENGENBACH.—Does vaccination interfere with immunization against diphtheria?

DR. LEAKE .-- No.

DR. HORTON.—Do you use one or two doses of diphtheria toxoid to immunize actively?

DR. HOYNE.—I use two doses and occasionally three. I question the value of convalescent serum in the prophylaxis of erysipelas. I think that it is valueless.

DR. KRAMER.—The use of any convalescent serum is likely to be misused. It may even cause us to miss an opportunity to study a disease. Good control studies should be made when using serum. Such information is now being gathered at serum centers. At present there is too much talk and little concrete information.

DR. PETERMAN.—These serum centers opened with a flare, accompanied by many false statements in the press; I think more harm than good may be done by indiscriminate use of serum. We question the value of a number of procedures now. Why add more? I feel that the value of serum will have to be settled in institutions since I feel that the reports coming from the outside are valueless.

CHAIRMAN TOOMEY.—Concluding this part of the discussion, I would state that the evidence does not favor the use of convalescent serum in either erysipelas or encephalitis, but it may have some value in mumps. Because I feel that erysipelas antitoxin neither stops the disease spread nor modifies the disease itself, I do not see how I could recommend its use as a prophylactic. The disease appears in patients with plenty of antitoxin present at the onset of the condition, in individuals who consistently have a negative Dick test, in individuals who no sooner are well than they may get another attack. We are now accumulating evidence to show that crysipelas is a disease which occurs only in individuals who have been previously infected with streptococcus infections, evidence which shows that the individual is left immune. This disease then is really nothing more than a giant local allergic manifestation to the entrance of organisms and their products, against which the individual already has plenty of active immunity in the adult and passive immunity in the child.

#### Passive Immunity Against Measles and Diphtheria Edgar E. Martmer, M. D.

Prophylaxis of Measles.—The modification or prevention of measles is recognized as a desirable procedure particularly in the case of small infants, weaklings, and children under five years of age.

The selection of individuals in which it is desirable to so modify an attack of measles or prevent it is entirely dependent upon the health of the individual, the possibility of his contracting complications, as well as where he lives.

There are several methods available for the prevention or modification of measles: convalescent serum, 4 to 10 c.c.; adult immune serum, 15 to 30 c.c.; convalescent whole blood, 10 to 30 c.c.; adult immune blood, 15 to 50 c.c.; placental extract, 2 to 6 c.c.

All of these preparations will modify or prevent the development of the disease. The degree of success attained by the use of these various agents is dependent upon several factors. Among the things influencing the degree of value of these materials are (1) potency of material employed, (2) dosage, (3) time of administration, (4) degree of exposure, and (5) immunity of individual exposed.

In an analysis of any immunizing program consideration must be given to the degree of exposure and the duration of such exposure.

Karelitz and Schick have shown that hospitals and institutions are usually inadequate for the study of measles prophylaxis because of the variations in the degree and length of exposure. They likewise demonstrate that the percentage of protection obtained in the home is in proportion to the hygiene of that particular home. The better the hygiene and care exercised, the more likely a satisfactory result will follow the use of prophylactic measures.

In addition, it was shown by these same authors that in homes of poor hygiene the percentage of protection secured was in direct proportion to the dosage of serum. The larger the dose the better the protection afforded.

Because of the varying conditions under which the various studies of the value of methods of preventing or modifying measles have been carried out it is difficult to compare the results. However, a review of the literature suggests that Table I is a reasonable estimate of the value of the various agents.

TABLE I

	TOTAL CASES	COMPLETELY PROTECTED	MODIFIED MEASLES	FAILURES
Adult serum	584	329 (56.4%)	139 (23.8%)	116 (19.8%)
Convalescent serum	1,627	1,227 (75.4%)	273 (16.8%)	127 ( 7.8%)
Placental extract	1,341	959 (71.5%)	321 (23.9%)	61 ( 4.6%)

From a study of this table one would be inclined to make the deduction that the first method of choice was placental extract, with convalescent serum second, and adult blood a relatively poor substitute for either of the first two mentioned.

It would seem that the figures for adult immune serum and placental extract should be more nearly the same when we consider that at least a portion of the placental extract is in fact adult serum. The probabilities are that, if the dosage of adult serum and placental extract were equal, the results would be more nearly alike. Tissue extracts in placental serum are probably responsible for reactions which have accompanied their use.

Aging the extract seems to influence favorably the reactions which follow its use. Unfortunately most of McKhann's cases (in which placental extract was used) were treated in institutions where the degree of exposure is relatively less than when the same procedure is carried out at home.

In addition, no figures are available so far as I know giving the comparison between placental serum and placental extract.

The method of testing potency employed in the commercial preparations now available is either the modification of measles in institutional cases or the determination of the diphtheria antitoxin potency of the extract. Both of these methods are unsatisfactory. Diphtheria antitoxin potency is not a good yardstick to draw conclusions as to the ability of a serum to modify measles. Likewise, the individual variations in degree of susceptibility must be taken into consideration, the average child in institutions not being comparable with the protected child in the home encountered in private practice.

In the light of our knowledge at present, it would seem that the most useful agent we have for the prevention or modification of measles is convalescent serum. The advantage of placental extract over adult serum or adult whole blood would seem to be (1) availability, and (2) a more standard mixture.

#### DISCUSSION

DR, GREENEBAUM,-Is convalescent serum of value in diphtheria?

DR. MARTMER.—Diphtheria antitoxin is so potent and reliable that it would seem useless to give convalescent serum when we have this material.

DR. GREENEBAUM.—I would like to have the subject of passive prophylaxis of measles by placental extract discussed. We get a lot of reactions with this material; I would like to know particularly about oral immunization.

CHAIRMAN TOOMEY.—In the county where you cannot see your patients often, you may give 1,500 units of diphtheria antitoxin to exposed children, but I do not see the value of such procedure in an urban practice where patients are seen more frequently.

QUESTION FROM AUDIENCE.—Is there a new antitoxin for diphtheria? I have hesitated to use antitoxin because of the possibility of sensitizing the patient. Will the new antitoxin prevent this?

CHAIRMAN TOOMEY.—Lederle has an antitoxin which they claim has been purified to the extent that all material causing reactions has been removed.

DR. S. H. ASHMUN (DAYTON, OHIO).—Placental material has given reactions in my patients. I have used adult serum with good results.

DR. SHAW.—I would suggest caution in the use of this new material; one should select cases carefully. I sometimes question the value of producing modified measles. Are we producing immunity?

CHAIRMAN TOOMEY .- I have seen second attacks in children thus immunized.

DR. KRAMER.-Second cases can occur in children. It may be a familial affair.

DR. MARTMER.—I would state that it would seem the best practice never to give diphtheria antitoxin when contact can be made frequently but always when the case cannot be followed (1,500 units). I have had reactions from placental extract and would prefer convalescent human serum in the prophylaxis of measles. From a practical standpoint I think children just passed school age should be allowed to get measles in the summertime, and I protect only the tuberculous child.

DR. R. CANNON ELEY (BOSTON).—The results in 2,133 patients who have received placental extract (immune globulin—human) in an effort to obtain modification or prevention of measles are of such a nature as to warrant the continuation of this procedure as an effective means of obtaining passive prophylaxis against measles. I cannot agree with Dr. Martmer in the statement that the results obtained with adult immune serum and placental extract are the same; in a group of 584 patients who received adequate amounts of adult serum for modification or prevention, 23.8 per cent were modified, 56.4 per cent were protected, while failures occurred in 19.8 per cent; of 1,341 patients who received placental extract for the same purpose 23.9 per cent were modified, 71.5 per cent were protected, while failures occurred in only 4.6 per cent.

The effectiveness of the extract may be influenced by several factors such as potency, degree of exposure, time of injection, age, and size of the patient. Needless to say, the uniformity of the results, i.e., modification or prevention, depends upon the same factors. Standardization of dosage has been based on the nitrogen concentration of the active fraction and not upon the presence of diphtheria antibodies, as it has been repeatedly shown that the content of measles antibody and of diphtheria antibody are not parallel. Karelitz and Schick have pointed out the influence that different types of exposure may exert on the appraisal of any prophylactic procedure employed in the treatment of measles. These factors had been duly considered in appraising the results obtained with placental extract, and, if one will

refer to the publications of McKhann and others, he will find the observations on the effectiveness of the extract divided into "intimate exposures" and "casual exposures."

The oral administration of the extract has been shown to reverse a positive Schick or Dick test, but it has not been advocated as a type of treatment in either diphtheria or scarlet fever. Nor has placental extract been suggested in the treatment of acute poliomyelitis, although the presence of antibodies in the extract has been demonstrated.

DR. MARTMER.—Children who get modified cases of measles may not develop immunity, and they may get a second attack after a subsequent exposure. There is a question in my mind as to whether season has something to do with modification. I do not see much modification when the material is used in late spring and early summer, but I have seen modification when the material was used in the early spring and late winter. Since convalescent diphtheria serum has only 4 units per cubic centimeter, the quantity that we would have to use to protect passively would be too large to be of any practical use.

# Passive Prophylaxis Against Poliomyelitis Sidney D. Kramer, M.D.

I should like to take this opportunity to review the problem of prophylaxis in poliomyelitis and attempt to evaluate both the experimental data and the results of several earnest efforts that have been made to apply specific prophylaxis in children. Let us first consider the reagents we employ in dealing with the experimental disease.

The virus of poliomyelitis has certain differentiating features from other viruses pathogenic to man: First, it is a virus of low infectivity. As compared with other viruses the average infective dose required to produce the disease in the susceptible animal is much larger than that of other viruses, notably, yellow fever. Second, it is a virus with low antigenic properties. The injection of relatively large amounts of the virus is required to induce an immunity at all comparable to that resulting from a frank crippling attack of the disease. In common with most viruses the antigenic response to poliomyelitis virus is a direct function of its virulence and the degree of its infectivity.

A number of us have, furthermore, presented data that suggest there exists in nature multiple strains of the virus that evince specific and different antigenic properties. While working with three strains (an Australian strain, a strain from New Haven, and our laboratory stock strain), we found that the immunity resulting from an attack of the disease was specific to each of the strains. We had two animals immunized against two of these strains, which, resisting their own virus intracerebrally, developed poliomyelitis when inoculated with these other strains. Furthermore, the serums of these animals neutralized the virus of the other two strains only after they had passed through a second and third attack of the disease, respectively.

There is strong experimental and epidemiologic evidence that so-called neutralizing substance present in the serums of animals or human beings who have passed through an attack of the disease, or in the serum of animals which have been actively immunized against it, is specific. The fact that the serums of normal monkeys regularly do not contain this substance and that the serums of essentially all animals and human beings who have passed through a frank crippling attack of the disease do contain it strongly suggests the specificity of this substance. Furthermore, Aycock and I have shown that the distribution of such neutralizing substance in the normal population coincides faithfully with the age distribution of the disease and parallels closely similar figures for the Schick test, thus adding indirect, but strong evidence of its specificity.

The term "neutralizing substance" refers to the property of the serums of convalescent and immunized animals and convalescent human beings to render an actively infective virus innocuous. That the action of such serum on a virus is in the nature of a neutralizing action rather than a destructive one is suggested by the experiments of Olitsky, Rhodes, and Long who by means of cataphoresis were able to recover active poliomyelitis virus at the anode from a completely neutralized mixture of virus and serum. This action of immune serum on virus is the basis for the therapeutic and prophylactic uses of immune poliomyelitis serum.

What experimental evidence have we, however, that such neutralizing action takes place in vivo? In reviewing the literature on the therapeutic and prophylactic use of human convalescent serum, one is struck by the frequency with which the early experiments of Flexner and his coworkers are quoted. These workers were able to protect their animals against intracerebral and intranasal inoculation of the virus from one to four days following intrathecal administration of immune poliomyelitis serum. These results are unique in that they are essentially the only clear-cut evidence of protection. Most that can be said for practically all other analogous experiments is that the results may suggest such protection but are not clear-cut or convincing.

Certainly our own experience with human serum, both human and monkey, as a therapeutic or prophylactic agent has been anything but reassuring. The time here is too limited to give the details of all our experimental efforts, but I should like to mention the results of a few of our experimental attempts at the prophylactic and therapeutic use of human convalescent serum.

We have failed to protect our animals against intracerebral inoculation of virus for even twenty-four hours by the administration of potent immune serum subcutaneously, intramuscularly, or intravenously in huge doses. Furthermore, the infectivity of the cords of animals treated during the incubation period seemed unaffected even when such large quantities of immune serum as from 5 to 16 c.c. per pound or from 10 to 30 c.c. per kilogram of body weight were administered.

In other experiments we made an effort to determine the fate of the immune substance. Animals were given subcutaneous inoculations of immune serum, were bled 6, 12, 24, 48, 72, 96, and 120 hours after administration, and neutralization tests were done on these samples. In only a single instance were we able to detect the presence of the neutralizing substance in such serum, and this occurred in a specimen of blood coming from an animal twelve hours following the administration of 75 c.c. of immune homologous or monkey serum. In animals receiving less serum, such immune substance could not be detected, nor could it be detected in animals receiving the larger dose longer than twenty-four hours following the administration of the serum. We failed completely to detect any trace of human serum even twelve hours after its administration.

We have modified our technic so that only small infective doses of virus were employed in the neutralization tests, but the results were essentially the same as when larger infective doses were employed. These results coincide with our failures to protect such animals against intracerebral inoculation of virus following the administration of serum, as well as our failures to alter the outcome of the disease by the administration of large doses of serum following intracerebral or intranasal inoculation.

A possible explanation for our failure to detect the presence of neutralizing substance in the serum of these animals suggested itself: namely, that the substance was so greatly diluted by the body fluids as to render its detection difficult or impossible. This seemed reasonable in view of the low titer of neutralizing substance in convalescent serum. When we were fortunate enough to obtain from Dr. Schaeffer in Dr. Park's laboratory, a small amount of concentrated hyperimmune poliomyelitis horse serum with a titer some 40 times that of human convalescent serum, we

repeated some of our protection experiments employing this serum. In a small series of 6 animals inoculated subcutaneously with 10 c.c. of this serum per kilogram of body weight, we were apparently able in one instance to obtain protection against intracerebral inoculation of a small but constant infective dose of virus five, but not six, days following administration. Dr. Schaester, independently, obtained the same result, even though he employed a larger infective dose of virus. Unfortunately, we have not been able to secure more of this serum.

This single positive observation, among the many negative observations, has stood out in our minds as a hope and encouragement that some such specific prophylactic agent will be developed. But realizing the vagaries of poliomyelitis virus and knowing that monkeys, although uniformly susceptible, may vary in the degree of susceptibility, we have been very hesitant in accepting this isolated observation as decisive evidence.

In spite of the many negative results and only the uncertain suggestions that some protection may have been obtained, the general feeling and urge has been to employ such serum for human prophylaxis, and there have appeared in the literature the results of a number of such efforts to confer protection by the administration of parental blood or human convalescent serum in epidemic areas. An analysis of these results brings out several interesting and important points, which serve to emphasize the caution which must be exercised in evaluating such data.

At this point, it might be well to consider some epidemiologic and clinical features of the disease so that we may obtain some notion of the conditions under which information may be obtained. In the first place, poliomyelitis is a disease of low incidence, indicating that many thousands of children must be inoculated before the value of any prophylactic agent can be determined. In the second place, the outcome of infection is not predictable. We have no way of telling at the outset whether the child will escape or be badly crippled. All that can be said is that studies of the outcome of large series of recognizable and diagnosable cases indicate that a half or more of the cases escape paralysis. This emphasizes the importance of including an adequate number of uninoculated controls in such a study. In the third place, although poliomyelitis is endemic in certain locations, the epidemic occurrence of the disease is unpredictable for any given area or district; thus, we are seldom prepared to take advantage of a situation at the outset on an outbreak.

Furthermore, the duration of an epidemic of poliomyelitis is seldom longer than three months. We are usually well past the first third of the outbreak before we realize that we are dealing with anything more than a sporadic occurrence of the disease in an endemic area. Unless by happy chance an adequate organization is present in the field to initiate and carry on an experiment in prophylaxis, from two to four weeks more are lost before the mechanics of the preparation for the experiment are under way. Since a certain interval of time is further required for the actual administration of the material in question and by the time such inoculations have been accomplished and allowance is made for the incubation period of the disease, the greater part of the epidemic is over, and the resultant information can apply only to the smaller and waning portion of the outbreak.

I should like to illustrate how the above mentioned factors function by analyzing two recent efforts to test the prophylactic value of immune poliomyelitis serum.

In the summer of 1932 the town of Bradford, Pa., was visited by an outbreak of the disease. At the suggestion of Dr. Brebner of Dr. Park's laboratory, the local health authorities in Bradford established a free clinic at which 15 to 20 c.c. of parental blood was administered intramuscularly to children.

The first case of poliomyelitis was reported on August 25 and the last case October 17. Twelve hundred children were inoculated at the clinic and about 100

more by private physicians. About 2,500 children of the same age group did not receive serum and constituted the control group. One case occurred in the immunized group, while 32 cases occurred in the control group.

At first glance these figures seem impressive, but a consideration of the epidemic curve and the time elements shows fairly clearly that information can only be obtained concerning the portion of the outbreak between about the first and the seventeenth of October, which constituted the milder and waning portion of the outbreak. Information is not available concerning the number of cases reported up to the first week in October.

Although there may have been a strong clinical impression that the blood had been of value, yet from the above analysis it must be seen that too little information was actually available to justify any conclusion.

Another similar effort to determine the prophylactic value of immune serum for poliomyelitis was carried out in Philadelphia by Stokes and his coworkers that same year. The rapid and efficient organization of the unit and the happy cooperation of the many local health and other agencies is a commendable example of a community health venture.

The first case of the disease was reported in July, but it was not until the middle of August that Philadelphia realized that it was in the midst of an outbreak of the disease, second only to the severe outbreak of 1916. The peak of the outbreak was reached the fourth week in August. The unit at the Children's Hospital in Philadelphia began to function on August 20 and thereafter for six weeks, or until the epidemic was over. During this time 1,341 children were injected with 60 c.c. each of parental whole blood. Other hospitals in Philadelphia cooperated in the effort, although human convalescent serum in smaller amounts was employed by some of these institutions in place of parental blood. The total number of children including those inoculated by other institutions was 2,179.

The incidence of the disease in the inoculated group was 1 to 363. The incidence for the same age group in the rest of the city was 1 to 555. From this analysis it must be fairly obvious that even less information is available from this study than from the Bradford effort. Since immunization of children began on August 20 and continued until the outbreak was over, there was a constant selection of children who probably would not have contracted the disease in any case, and at the same time they were excluding those children who contracted the disease during this portion of the outbreak.

Effective clinical trial of the prophylactic value of an agent depends on the presence of a well-organized unit at the outset of an outbreak. With such a unit constantly on the alert for the early appearance of cases in unusual numbers, information concerning a significant portion of the outbreak might be obtained. However, in view of the unpredictableness of epidemics of poliomyelitis, much time will unquestionably pass before sufficient data will have been accumulated.

Recently, Armstrong and Harrison, Sabin, Olitsky and Cox, and Schultz and Gebhardt have suggested that effective blocking of the virus at the nasal mucous membrane in the experimental animal may be accomplished by a variety of chemical substances. Should such chemicals prove effective, it must also be established that the prolonged use of such substances will have no injurious effect on the nasal mucous membranes.

Furthermore, since the protection afforded would be a transient one, susceptibles would remain susceptible to future exposures later in life. Since immunization and protection to the disease is the result of exposure to the virus, withholding such exposure and immunity to a later period in life would be similar in effect to converting an urban population to the status of a rural community, where exposures and disease

come later in life. Therefore, it appears to us that, since exposure to infection is a direct function of concentration of population or of irreducible human contact, a more logical approach to the control of the disease is through active immunization.

#### DISCUSSION

CHAIRMAN TOOMEY.—It is your opinion then that the use of poliomyelitis convalescent serum is questionable. What would you do if your own child were exposed to poliomyelitis?

DR. KRAMER.-It is very uncertain as to what I would do.

CHAIRMAN TOOMEY.—I question the evidence which tends to show that there are multiple strains of poliomyelitis virus, but this is a minor point and not germane to our discussion. I agree with Dr. Kramer about the use of nasal sprays, not because their use may do harm to the nasal mucosa, but because there is no conclusive evidence that the disease enters the human being by way of the nasal pathway. If the virus of the disease enters the human being by way of the gastro-intestinal tract, as I believe it does, then such procedures would be valueless.

DR. HOYNE.—I favor the use of convalescent serum in poliomyelitis on the ground that it does no harm and it may do some good. Some say it must be used in preparalytic stage. Some say 87 per cent will never develop paralysis in any group of cases. The temperatures will not only go down in convalescent serum treated cases but also in the control cases—the hospital case. Perhaps the response is nonspecific and due to care alone. This subject brings out the difficulty of evaluating any serum. I believe the patients should get more serum, though never intraspinally. If it is given intravenously, the children do a lot better since most physicians see the case at height of paralysis, and it does not spread further. It is hard to draw definite conclusions.

DR. MARTMER.—I believe that convalescent poliomyelitis serum has no value; or, if it has any, it must be given intravenously and in large doses and in the early case. The public has been erroneously educated as to its value as a prophylactic. If the exposed child receives his convalescent serum the parent ceases to worry, and the child is exposed further because of the false sense of security. One should never use the material intraspinally since it may set up sterile meningitis.

DR. R. H. McBRIDE (Sioux City, Iowa).—One should ever be cautious about the effect on the public. One should not by selling something of questionable value lessen confidence of the public in these things that are of proved value.

DR. KRAMER.—I had the clinical impression that convalescent serum is of value, until we studied our control groups. Convalescent serum will perhaps do no harm, but it is possibly of no value; use it if you want to do so. Remember that no control group has proved its value, and in prophylaxis it certainly is of no use. Tannic acid in the nose will do a great deal of damage and harm, especially when it can be secured by the public. This holds true for all the other chemicals bought over the drug counter by the public.

Dr. Maxwell P. Borovsky, Chicago.
Dr. Matthew Winters. Indianapolis, Ind.
Recorders.

## MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

The Meeting of the Executive Board was called to order at 11 A.M., Nov. 28, 1936, at the Georgian Hotel, Evanston, Ill. Those present were Dr. L. R. DeBuys, president; Dr. Philip Van Ingen, vice president; Dr. Clifford G. Grulee, secretary; Dr. Louis C. Schroeder: Dr. Edward C. Mitchell; Dr. Henry F. Helmholz; and Dr. Edward B. Shaw.

The following applicants were elected to membership:

#### REGION I

- Dr. Samuel Ash, Newark, N. J.
- Dr. Joseph S. Baird, Pittsburgh, Pa.
- Dr. Mary Knott Bazemore, Merion, Pa.
- Dr. Israel Binder, Philadelphia, Pa.
- Dr. Randolph K. Byers, Boston, Mass.
- Dr. Albert Graham Davis, Utica, N. Y.
- Dr. Sarah S. Deitrick, Washington, D. C.
- Dr. James M. Dobbins, Long Island City,
- Dr. Katharine G. Dodge, New York,
- Dr. Lawrence C. V. du Busc, Elizabeth,
- Dr. R. Cannon Eley, Boston, Mass.
- Dr. Bernard Fein, Newark, N. J.
- Dr. Elias Freidus, Long Beach, N. Y.
- Dr. Charles R. Goldsborough, Baltimore,
- Dr. Francis J. Gustina, Buffalo, N. Y.
- Dr. Jonathan P. Hadfield, Fall River, Mass.
- Dr. Rachel L. Hardwick, Boston, Mass.
- Dr. George Heller, Englewood, N. J.
- Dr. Arthur Hevman, Newark, N. J.
- Dr. Alice K. Higgins, Rockville Center, N. Y.
- Dr. Harold L. Higgins, Boston, Mass.
- Dr. Frederick H. von Hofe, East Orange, N. J.
- Dr. John Williams Holmes, Philadelphia,
- Dr. Frederic S. Huntington, Scranton, Pa.

- Dr. A. Elizabeth Ingraham, Hartford,
- Dr. Earl Francis Kelly, Pawtucket, R. I.
- Dr. Dorothy M. Lang, White Plains, N. Y.
- Dr. Abraham M. Litvak, Brooklyn, N. Y.
- Dr. George C. Ludlow, New London, Conn.
- Dr. Harry Berst Mark, Riverton, N. J.
- Dr. Paul J. McGuire, Homestead, Pa.
- Dr. Stephen Dow Mills, Westfield, N. J.
- Dr. Gordon Manace, Toronto, Ont., Canada.
- Dr. Marion S. Morse, Endicott, N. Y.
- Dr. Alfred A. Nathans, Brooklyn, N. Y.
- Dr. Rae V. Nicholas, Philadelphia, Pa.
- Dr. William J. Orr, Buffalo, N. Y.
- Dr. Warren Ripley, Montclair, N. J.
- Dr. Harvey O. Rohrbach, Bethlehem, Pa.
- Dr. Frank E. Roth, Hartford, Conn.
- Dr. Isadore B. Rothstein, Newark, N. J.
- Dr. Harry Benj. Silver, Newark, N. J.
- Dr. Charles I. Solomon, Meriden, Conn.
- Dr. Susan Page Souther, Hartford, Conn.
- Dr. Harry A. Spigel, Washington, D. C.
- Dr. Lucy Porter Sutton, New York, N. Y.
- Dr. Abraham Tow, New York, N. Y.
- Dr. Jacob Wallace, Boston, Mass.
- Dr. Stanley M. Wershof, New York,
- Dr. Luvia Willard, Jamaica, N. Y.
- Dr. Israel J. Wolf, Paterson, N. J.

#### REGION II

- Dr. M. Vaun Adams, Mobile, Ala.
- Dr. John Edmund Ashby, Dallas, Texas. Dr. John Mason Bishop, Roanoke, Va.
- Dr. James W. Britton, Anniston, Ala.
- Dr. Nicholas B. Cannady, Dothan, Ala.
- Dr. Robert M. Finks, San Angelo, Texas.
- Dr. Philip C. Elliott, Nashville, Tenn.
- Dr. Maurice Fliess, Clifton Forge, Va. Dr. Thomas Archer Gibson, Winchester,
- Dr. A. C. Gipson, Gadsden, Ala.
- Dr. R. C. Goolsby, Jr., Macon, Ga.
- Dr. David W. Goltman, Memphis, Tenn.
- Dr. J. S. Hunt, Charlotte, N. C.

Dr W. Eugene Keiter, Kinston, N. C

Dr. Charles L Kennon, Miami, Fla.

Dr. Thomas E. Oast, Portsmouth, Va.

Dr. Jack Furman Perkins, Dallas, Texas.

Dr Sam Phillips, Little Rock, Ark.

Dr. William Ewing Sinclair, Orlando, Fla.

Dr. Henry S Stern, Richmond, Va

Dr. T. D. Walker, Jr., Newport News, Va

Dr. Charles Wallis, Little Rock, Ark.

Dr. Benjamin Rappaport, Evanston, Ill.

Dr. C. R. Rittershofer, Cincinnati, Ohio.

Dr. Geneva Shong Rothemund, Columbus,

#### REGION III

Dr. Katherine Bun, St. Louis, Mo.

Dr Emanuel B. Brandes, Cincinnati, Ohio.

Dr John C. Sandford Brown, Saskatoon, Sask., Canada.

Dr Isador M. Epstein, Chicago, Ill

Dr A. J. Fletcher, Danville, Ill

Dr. I. H Kass, Toledo, Ohio

Dr. Bertrand I. Krehbiel, Topeka, Kan.

Dr Ralph H. Kunstadter, Chicago, Ill.

Dr Benjamin M. Levin, Chicago, Ill. Dr Waldo E. Nelson, Cincinnati, Ohio. Dr. Alwin C. Rambar, Chicago, Ill. Dr. Irwin Rubell, Chicago, Ill

Dr. A. W. Pinkerton, Lima, Ohio.

Dr. Arthur S. Sandler, Chicago, Ill. Dr. Martha Souter, Indianapolis, Ind.

Dr. Hart Edgar Van Riper, Madison, Wis

Dr Simon A Wile, Chicago, Ill.

#### REGION IV

Dr. Harry R. Carson, Phoenix, Ariz.

Dr Einor H Christopherson, San Diego, Calif.

Dr. Thomas W. Cornwall, San Francisco, Calif.

Dr Darcy M. Dayton, Tacoma, Wash Dr William C. Deamer, San Francisco,

Dr Frederick R. Fischer, Spokane, Wash

Calif.

Dr. A. Lawrence Gleason, Oakland, Calif.

Dr Paul H. Herron, Spokane, Wash

Dr. Robert S Leet, Oakland, Calif.

Dr. Donald C Marshall, San Francisco, Calif.

Dr Emmett E Sappington, San Francisco, Calif.

Dr. Frank M. Sprague, Boise, Ida.

Dr. G D. Carlyle Thompson, Boise, Ida

Dr. Arthur E. Varden, San Bernardino, Calif.

Dr Lynn B. Vaughan, Long Beach, Calif.

The next Annual Meeting will be held at the Waldorf Astoria Hotel, New York City, June 3, 4, and 5, 1937. The following program was decided on:

June 3, Morning—Round tables
Afternoon—Exhibit demonstrations

June 4, Morning—Business meeting President's address

Two outstanding papers

Afternoon-Panel discussions

June 5, Morning-Repetition of round tables

The following subjects were tentatively chosen for the round table discussions:

Adolescence
Anemia of the newborn
Asthma
Childhood psychiatry
Common skin diseases
Diabetes
Eczema
Eve diseases—squint

Gonococcus infection
Meningococcic meningitis
Nephritis
Poliomyelitis
Sedimentation rate
Treatment of empyema
Vitamins.

Regarding the round tables, it was decided that a secretary from each group registered for each round table be chosen and the same plan be carried out as last year.

The following subjects were tentatively chosen for exhibit demonstrations: "In travenous Therapy," "Unusual Diseases of the Bone," and "Urinary Infections"

The exhibit demonstrations are to cover a period of three quarters of an hour each: half hour for the demonstration and fifteen minutes for questions from the floor. A man may be interrupted at any time during the demonstration with questions from the audience

The following subjects were tentatively chosen for panel discussions: "Present Status of Active Immunization Against Scarlet Fever" and "Present Status of Active Immunization Against Whooping Cough" The panel discussions are to be for a period of one and one half hours each with fifteen minutes" intermission

The financial report and the budget were approved. It was moved, seconded, and carried that \$5,000 be taken from the checking account and placed in a saving-account in another bank.

Dr. Grulee reported that the Committee on School Health and School Health Education is preparing an extensive investigation

Report of the Committee on Clinical Investigation and Scientific Research regarding the offer of the Borden Company to give to the American Academy of Pediatrics directions for the use of the rights of the patent of the Borden Company for freezing breast milk, was read and was approved. The report follows:

Report of the Committee on Clinical Investigation and Scientific Research on the Offer of the Borden Company to Give to the American Academy of Pediatrics Directions for the Use of the Rights of the Patent of the Borden Company for Freezing Breast Milk

On Jan 27, 1936, Dr. James A. Tobey, Director of the Department of Health Service of the Borden Company, wrote to the American Academy of Pediatrics that the Borden Company proposes to make this process available without charge to ethical hospitals having proper facilities for its use. In order to license such accredited hospitals, it is proposed that a medical board be set up consisting of Dr. Paul W. Emerson, two members appointed by the American Academy of Pediatrics, and one member appointed by the Council on Medical Education and Hospitals of the American Medical Association, the secretary of the committee to be Mr. Raymond Hertwig, now associated with the Borden Company, who would carry on all active work in accordance with the policies set by this medical board. The board would not represent this company but would merely be an impartial group of distinguished medical scientists concerned with a process that seems to offer a real contribution to certain aspects of the science of pediatrics.

This request was referred to the Committee on Chinical Investigation and Scientific Research with power to act

A conference was held with Dr. Tobey and after the conference he wrote a letter, May 29, 1936, saying that in order to do this, it would be desirable to have an impartial medical committee which would license prospective users of the process. Such a committee would not represent the Borden Company but would be selected and appointed by some such logical agency as the American Academy of Pediatries. The Borden Company will assign to the committee a competent secretary to carry out these policies and to undertake all necessary administrative activities. He said that the Borden Company had in mind for this duty Mr. Raymond Hertwig

In a later conference Dr. Tobey stated that if the Academy did not wish to have the services of Mr. Hertwig and cared to administer the use of this patent through its own office there would be no objection. He explained that this process was legally patented by the Borden Company and that the Borden Company desires no revenue from it and is willing to turn over all rights in process to any authoritative medical body which could then investigate and license qualified and reputable hospitals or groups of medical men, or welfare agency under medical supervision or guidance. Licenses have already been given to

- a. Mother's Milk Bureau under the Children's Welfare Federation of New York City, Dr. Carl Laws of Brooklyn, Chairman of the Medical Advisory Committee.
- b. The Memorial Hospital of Houston, Texas, Mr. Robert Jolly, Superintendent.
- c. The method is being used by the Directory for Mother's Milk in Boston, under whose auspices and through whose initiative the process was developed, although the Borden Company states that they bore all the expense of this development. No license has, as yet, been signed for its use by this Directory because of certain disagreements between the Directory and the Borden Company.

Applications for its use have been made by the California Babies' Hospital of Los Angeles, which has requested the sole license for the state of California. Inquiries have been made by Dr. Weigand, of Omaha, Neb.; the Harlem Hospital of New York; a hospital in Cleveland; Dr. Moore, of Dallas, Texas; and others.

We understand that the organizations which are now using the process for freezing breast milk, with or without licenses, are as follows:

Directory for Mother's Milk, Inc. 221 Longwood Avenue Boston, Mass.

Dr. S. Graham Ross Royal Victoria Maternity Montreal, Canada

Dr. Fraser
Fraser Hospital
Royal Victoria Maternity
Montreal, Canada

Dr. Alfred J. Scott
Dr. Robert Ramsey
California Babies' Hospital
Los Angeles, California

Mr. A. R. M. MacLean, Technical Director Eastern Dairies, Limited 7460 Upper Lachine Road Montreal, Canada

The Registry for Mother's Milk Forbes & Halket Streets Pittsburgh, Pa.

This offer of the Borden Company brings up again a specific example of the problem of commercial patents as applied to health and welfare. In the opinion of your committee there is not yet enough data available to make it clear what bearing this offer of the Borden Company has on the general problem.

The offer of the Borden Company seems to be a very gracious action with a highly ethical purpose, and during our conversation with Dr. Tobey that seemed to

be the purpose back of the offer. The committee believes that if such an offer were accepted, the administration of this patent should be solely in the hands of the Academy of Pediatrics and entirely separated from the Borden Company. It does not believe that this patent could be satisfactorily administered and the public protected if it were handled in the manner first suggested.

If the Academy undertook to handle such a patent it would necessitate

- a. A committee which would be able to visit and investigate all the applications for the use of the patent. In one instance the Borden Company has thrown down a request, after investigation.
- b. It would necessitate overseeing the use of the patent to see that the methods of freezing milk were done properly and the directions carried out. This would require periodic inspections.
- c. It would probably require taking to court any infringement of the patent and protecting it.

In our opinion, the supervision of this work would necessitate considerable administrative expense. Your committee, therefore, reports that in its opinion the present organization of the Academy of Pediatrics is not such that it can undertake the responsibilities and the expense involved in accepting the administration of this patent.

Respectfully submitted,
(Signed) Fritz B. Talbot, Chairman.

Henry F. Helmholz.

The requests of Dr. Maynard Ladd, of Boston, and Dr. Ann Martin, of Hayward, Calif., to be placed on the Emeritus list were granted.

Dr. Carroll E. Palmer, of Washington, D. C., was elected to Associate Fellowship at the request of Dr. L. Emmett Holt, Jr.

A letter was read from Dr. Charles Bradley, of East Providence, R. I., requesting approval of the Academy of the Emma Pendleton Bradley Home. It was decided that the Executive Board was in no position to do this and that his request should be referred to the Committee on Medical Education.

The letter from Dr. Frederick B. Miner, of Flint, Mich., regarding the Academy's interpretation of the word "crippled" was then taken up. It was decided that a much broader interpretation should be put on the definition of this word than is usually done by orthopedic surgeons.

The letter of Dr. Julian P. Price, of Florence, S. C., regarding a publication for the education of general practitioners, was discussed. It was decided that the Academy could not undertake such a publication at the present time, since the Executive Board did not feel that it was feasible.

The request of Mr. Max Freeman, of Los Angeles, Calif., that the Academy approve his institute, was not granted, since the Executive Board felt that the Academy was in no position to do this.

The question of associate chairmen of regions and the method of their selection was discussed. It was decided to leave with Dr. Helmholz the formulation of these ideas and submit them to the membership at the next annual meeting after approval by the Executive Board.

# MEETING OF REGION IV OF THE AMERICAN ACADEMY OF PEDIATRICS

The fifth annual meeting of Region IV of the American Academy of Pediatrics was held in San Francisco on October 22-24, 1936. While exact attendance figures are not available, owing to incomplete registration, it is believed that not less than 90 per cent of the membership of the region was in attendance, including representatives from all the states and the Territory of Hawaii. In addition, many nonmembers were present, and the average attendance at the various sessions was about one hundred. Abstracts of papers on the program follow immediately. Dr. Karl F. Meyer, professor of bacteriology of the University of California and head of the Hooper Institute for Medical Research, gave, by invitation, an exhaustive and valuable review of the diseases caused by the neurotropic viruses. The round table discussion of prophylaxis of communicable diseases attracted general interest. The annual dinner, held at the Concordia Club and arranged by Dr. Cohn and Dr. Dearing, was well attended and successful. Dr. Joseph B. Bilderback was toastmaster, and brief addresses were given by Dr. Clifford G. Grulee, secretary and treasurer of the Academy, Dr. Henry Dietrich, and others. It was tentatively decided to hold the 1937 meeting at Del Monte, Calif.

#### Fetal Respiratory Movements. Barnet E. Bonar, M.D.

This is a discussion of a method to evaluate the effects upon the fetus of obstetric analgesics and anesthetics.

The status of present-day obstetric analgesia and anesthesia was discussed critically, and the lack of decided progress in this field was pointed out. The methods that have been used to evaluate the effects of obstetric analgesia and anesthesia were outlined. It was stated that the criteria used to determine the effects of these preparations upon mother and child, with few exceptions, were so grossly inadequate that accurate deductions were impossible. The clinical method has so far given little information of value. From the maternal standpoint hysterographic methods should be used if authentic data are to be had. In respect to the fetus the method described by Rosenfeld and Snyder of visualizing the fetal respiratory movements deserves more attention. It consists of exposing the uterus of the experimental animal after transection of the spinal cord and observing with the naked eye the effects of the various drugs upon these movements. Motion pictures may be taken. This method was described and color motion pictures shown illustrating the respiratory movements through the exposed but intact uterus in the rabbit and dog. In order to study more closely the types of respiratory movements, pictures were taken of the fetuses lying in the transparent amniotic sac. Two types of respiratory movements were observed, and the inhibiting effects of ether and some of the basal analgesics upon these movements were noted. The possibilities of studies of this nature were pointed out, and it was suggested that the scientific accuracy of this method could be enhanced if an apparatus for registering these movements effectively over a longer period of time could be devised. Efforts are being extended along these lines at present so that more information can be obtained regarding the effects upon the fetus of analgesics, anesthetics, and oxytoxics used in childbirth, as well as investigations made upon the effect of carbon dioxide concentrations upon the fetus in utero.

# Roentgen Ray Treatment of Acute Cervical Adenitis. Samuel Hurwitz, M.D., and Sidney N. Zuckerman, M.D.

Sixty-two children with acute cervical adenitis were treated with small doses of reentgen rays (about 80 r.). Resolution occurred in 52 (83.9 per cent) cases, while 9 (14.5 per cent) cases terminated in suppuration. In a group of 21 adequately con-

trolled, hospitalized patients, who were irradiated, 17 patients (81 per cent) were cured as opposed to 10 patients (58.8 per cent) treated by other measures. Suppuration resulted in 3 children (14.3 per cent) treated with roentgen rays as opposed to 7 (41.2 per cent) in the control group. Rapid subjective improvement and accelerated termination is a striking feature of roentgen therapy. Radiation is most beneficial in the early stage of inflammation in which absorption is the usual final result. If suppuration is already present before treatment is started, necrosis is hastened and early centralization of the infection results.

#### Exanthem Subitum. Lloyd B. Dickey, M.D.

Exanthem subitum is a clinical entity, of as yet unknown etiology, but having no known relationship to other common exanthems. Most cases occur during the first two years of life, and in San Francisco it is probably the commonest exanthem under one year of age. The most constant feature of the symptomatology is a three-or four-day prodromal period of fever which disappears by crisis, the macular rash always occurring after the crisis. Numerous other symptoms may be present, and convulsions at the onset are not uncommon. The blood count at some time during the course shows a leucopenia, with relative increase in the lymphocytes. The patient should be observed at least forty-eight hours after a fall of the temperature suggesting this disease, for the rash which makes the diagnosis. The rash before its appearance to the unaided eye, may sometimes be seen under the ultraviolet light as long as twenty-four hours before the crisis.

#### Epidemic of Unknown Etiology. Myrl Morris, M.D.

An epidemic occurring in a foundling home in babies under three months of age is reported. The author suggests from the symptoms found in the infants that the invader might be a filtrable virus with an affinity for the autonomic nervous system.

A résumé of the pathologic findings in six autopsies is included in the report.

#### Vitamin C in Rheumatic Fever. James F. Rinehart, M.D.

The experimental basis for the concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection was briefly reviewed. Following this, studies on the metabolism of vitamin C were reported. It was shown in confirmation of the studies of Farmer and Abt that the concentration of vitamin C in the blood plasma is an accurate index of the immediate nutritive state relative to vitamin C. The "normal" fasting plasma vitamin C level in children we consider to range from 0.7 to 1.5 mg. per 100 c.c. Levels below 0.5 mg. are considered low. Analyses were reported in rheumatic fever and control groups. A series of 21 cases of acute rheumatic fever gave values which ranged from 0.13 to 0.68 mg. with an average of 0.39 mg. per 10 c.c.; 76 per cent were in the range considered to be low, i.e., below 0.5 mg. In a control series of children admitted to the University of California Hospital for tonsillectomy, values ranged from 0.19 to 1.57 mg., the average being 0.83 mg.; 74 per cent gave values above 0.5 mg. Almost identical values were found in a series of 19 cases of miscellaneous nonrheumatic infections. Without reference to the mechanisms creating the depletion, these data are considered to be in accord with the concept that vitamin C deficiency may be a factor in the etiology of rheumatic fever.

#### Fulminant Streptococcic Sepsis in Infancy. John Mott Rector, M.D.

A syndrome of acute streptococcic sepsis in infancy is described in which death follows the onset of a bacteremia with such rapidity that localizing signs rarely have time to appear. Of interest etiologically was the finding of active rickets

among most of the patients. Although there are various portals of entry for this type of infection, the most common entrance is through the pharynx and communicating cavities.

There is a fairly well-defined uniformity in the pathologic changes observed, the most typical feature being early interstitial bronchopneumonia. Common symptoms include hyperpyrexia, vomiting, diarrhea, meningismus, and severe convulsions. While positive blood cultures offer the best confirmatory evidence, it is possible to make the diagnosis clinically if the condition is kept in mind.

### The Practice of Pediatrics in Hawaii. Joseph Palma, M.D.

Some of the interesting features of the practice of pediatrics on "the loveliest fleet of islands anchored in any ocean" are presented. The similarity with mainland procedures was noted in infant feeding and supervision, and the moderate course of contagious and infectious diseases was discussed. Attention was directed to the absence in Hawaii of any of the group of tropical diseases and malaria. A symptom-complex known as febricula hawaiiensis was identified as epidemic vomiting disease, recently described by Greenthal. The first clinical findings of leprosy observed in children were discussed in some detail, with emphasis on the neurologic rather than on the dermatologic character of the early lesions. Pertinent comment upon certain trends in modern pediatric practice was presented in conclusion.

#### Some Pathologies of Light. Lloyd E. Hardgrave, M.D.

A case of hydroa aestivale vacciniforme with porphyrinuria with a demonstration of the spectral region of sensitivity was presented, the patient being photosensitive and manifesting skin lesions when exposed to sunlight. The patient reacted with a marked erythema to wave lengths between 3,200 Å and 4,500 Å, indicating a hypersensitivity to this radiation, which is that most strongly absorbed by the porphyrins. It has been, however, impossible thus far to reproduce the hydroa lesions experimentally with these or any other wave lengths. The patient was treated biweekly with quartz-mercury are radiation, which contains relatively little of these wave lengths, for many months, which produced no abnormal reaction but produced a healthy normal coat of tan, and rendered the patient less vulnerable when exposed to natural sunlight.

Other evidences of photosensitivity in man were described, particularly those following the oral administration of dye substances; and in animals, of some foods and plants such as buckwheat and St. John's wort.

More pertinent data following this study has been the observation that although the radiations which produce erythema, tanning, and vitamin D formation are in the same zone, i.e., shorter than 3,200 Å, they are not identical, and it is quite probable that many patients that have been given tanning by quartz-mercury are lamps have not had a simultaneous stimulation of their vitamin synthesis and that such lamps would bear more careful analysis of their radiation wave lengths, thus more accurately establishing their therapeutic value.

An appeal was made to all pediatricians to analyze carefully the various sources from which their patients received vitamin D before prescribing wholesale treatments with the mercury are lamps or sun baths lest certain individuals be found to be receiving a definite pathologic overdosage of this particular vitamin.

## "Stippled" Formation of Epiphyses in Hypothyroidism. By William A. Reilly, M.D., and Francis Scott Smyth, M.D.

Some of the more severe cases of hypothyroidism show a peculiar stippling in the formation of the epiphyses, principally in the long bones, occasionally in the vertebrae. These are usually bilateral and occur in several different areas, in the following order of frequency—the heads of the femurs, humeri, and the lower end of

the radii. The lesion is not destructive, responds readily to thyroid therapy and usually results in normal epiphyses if treatment is started early in the formation. This is not a Legg-Perthes' disease.

#### Phlyctenulosis. Harold K. Faber, M.D., and Lloyd B. Dickey

This local affection of the eye occurs almost exclusively in individuals with past or present tuberculous infection, as shown by the presence of positive reactions to tuberculin. Furthermore, the reactivity is much greater than the average as judged by the greater average size of the reaction. Clinically, signs and symptoms of active tuberculosis are usually, but not always, absent. Therefore, it seems unlikely that the ocular disorder is produced by endogenous tuberculin or tuberculous products acting on a sensitized conjunctiva, but much more probably by tuberculous material (droplets, dust, etc.) gaining access to the eye from without in tuberculin-hypersensitive individuals. While animal experiment is inconclusive, experience with the Calmette test has shown conclusively that tuberculin dropped in the eye in sensitive individuals will frequently produce phlyctenulosis and provides experimental confirmation of the theory propounded.

If these conclusions are correct, phlyctenulosis is a direct indication of contact with tuberculosis and has an important public health aspect, since it makes a search for the source of contact imperative.

## MEETING OF THE STATE CHAIRMEN OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting of state chairmen of the American Academy of Pediatrics was called to order at 8 p.m. in the Hotel President, Kansas City, Mo., by the president, Dr. Henry Dietrich, May 11, 1936.

PRESIDENT DIETRICH.—The meeting of state chairmen will please be in order. I shall ask Dr. Eliot to preside and conduct the discussion.

Dr. Martha Eliot assumed the chair.

DR. ELIOT.—The Committee on Child Health Relations has a brief report to make, which I shall read to you at this time. (Dr. Eliot read the report.)

I would like to add one or two facts with respect to the Social Security Act, which have not been included in this brief report. In the first place, in regard to the program for crippled children, thirty-nine states have submitted plans to the Children's Bureau. Under the program for child welfare services, which has to do with "dependent, neglected, and homeless children, and children in danger of becoming delinquent." plans have been submitted by the state departments of public welfare of twenty-nine states, and of these, twenty-five or twenty-six have been approved. The program for crippled children is new in many of the states, as is also the child welfare program.

The maternal and child health plans began to come to the Children's Bureau before January 1, 1936. As soon as the Social Security Act became law in August, 1935, a few states began to develop their programs, but until it was known that money was to be available, the real stimulus for developing these plans was not very great. The majority of the plans were submitted in January and February just before the passage of the appropriation act which provided the money for the grants.

SECRETARY GRULEE.—What is the interpretation of the Bureau of the term "crippled children"?

DR. ELIOT.—I am glad that question was asked. In the federal act the words are "crippled children or children suffering from diseases that may lead to crippling." A definition was not given in the act, purposely, I believe, to allow for a broad interpretation based upon individual state laws. It is the intention of the Children's Bureau to interpret the term broadly, recognizing that a child may be crippled not only by poliomyelitis and other orthopedic conditions but also by disease of his cardiac muscle. Many of the states already have definitions in their state laws, but these definitions vary to such an extent that it is felt to be a mistake to attempt at this time to lay down a single definition.

SECRETARY GRULEE.—The Executive Board at its meeting yesterday passed a resolution stating that it regarded the word "crippled" in that sense as meaning physically handicapped (any physical handicap).

DR. ELIOT.—Of course, if you interpret the term "crippled" so broadly as to include any physical handicap, a child with one carious tooth might be included. I am exaggerating now, but that illustrates some of the questions that may come before us. For instance, shall we include as crippled children those who need tonsillectomies?

SECRETARY GRULEE.—That depends upon the interpretation of the term "handicap."

DR. ELIOT .- What are the conditions that handicap a child?

DR. DIETRICH.—We had in mind the cardiac condition and conditions of that sort. Ordinarily a crippled child means a crippled child from an orthopedic standpoint.

DR. ELIOT.—I talked only today to an orthopedic surgeon and a pediatrician from the same state, both of whom are interested in working out plans under the crippled children's section. I told them they should get together with the state agency and work out a plan that would come under their state law and the provisions of the federal act.

DR. PAUL C. CARSON (KANSAS).—In connection with the crippled child program in Kansas, the matter of tonsils was terribly abused the first two or three years, and the funds available were used for cases like tonsillectomies.

DR. ELIOT.—The total amount of the grant in aid to crippled children is \$2,800,000. All of it must be matched by the state. The total, you see, is not a very large sum of money, and most of the states appreciate that it should be conserved for children in the greatest need.

DR. MAURICE L. BLATT (ILLINOIS).—May I ask whether the interpretation regarding cardiac disease is to be broadly applied? It seems to me the large problem in Illinois is care of children with cardiac conditions, far larger than the orthopedic problem. We have adequate beds for orthopedic cases. We have anything but an adequate number of beds for cardiac cases. Do you feel we might utilize funds for care of cardiac patients?

DR. ELIOT.—I see no reason why the people who live in any given state and think one type of crippling condition is more urgent than another should not go to the state agency and urge whatever they think is the right procedure in that particular line. The question of inclusion of children with cardiac disease will vary from state to state and depend to some extent at least on the prevalence of the disease. When a state agency has asked what cardiac conditions may be included as "crippling," the reply has usually been that acute and early cases of the noncustodial type would seem to be the type that should be included. If the

child needs custodial care, treatment under this part of the act does not seem to be justified. The real purpose of the act is to save children from severe crippling

DR BLATT—The situation we have to meet is that this cannot go on unless some amount of custodial care is provided. In Chicago it is limited because of the transportation of children with cardiac discrete to a central school. In the rural community, even this inadequate service is lacking, and many children are handicapped by lack of education because of lack of custodial care.

DR ELIOT — You mean without boarding one. Let me say that the money under the crippled children's program is not for education. That ought to be clearly understood. Let us suppose a child who has recovered from poliomyelitis must be kept away from his home and near a cen'er where he can receive physical therapy. Such a child can be given boarding home care which may be paid for from the grants under the act.

DR LEE FORREST HILL (Iow 1)—I take it that it is your wish and the wish of the Committee on Child Health Relations that the state chairmen in the various states take a fairly active pirt in the administration of this Social Security Act. There are many states, particularly the state in which I live, where the administration of the act is under the direction of the state department of health.

I wonder what provision is to be made for us to appoint members to cooperate with health departments without their willing acceptance of such committee appoint ments. Is the Academy or are you going to advise the state health departments in the various states who have already formulated a program and are already working that such appointments are going to be made?

There is also another phase in which I am interested in connection with the crippled children program in Iowa I understand the ruling has been made in that state that crippled children are under the department of the Board of Education and not under the department of the Board of Health and that this work will be done at the state university, as a function of the Board of Education and not of the Department of Health.

DR ELIOT.—The state health department has been designated by Congress as the official agency to administer the maternal and child health program. Similarly the part of the program that has to do with general public health is administered by the state department of health

SECRUTARY GRULEE -Was it not to be in consultation with the medical, nurs ing and other groups?

DR ELIOT—The act itself outlines seven requirements that must be fulfilled before a state plan can be approved by the Children's Bureau. The sixth of these conditions is that the plan must show cooperation between the health department and medical, nursing and welfere groups and organizations. Our field consultants have discussed with the state agencies the intent of this requirement and have pointed out the importance of cooperation with state medical societies, the Academy of Pediatrics, the state committees on maternal welfare, etc. The state health department, however, when it submits to the Children's Bureau its plan, must show how this cooperation with medical groups and organizations is to be accomplished

In a majority of cases, the state health department has appointed an advisory committee and in a good many instances the state chairman of the Academy has been appointed on this committee. In all cases a list of organizations represented on the committee is given in the plan and in many instances the names of the individuals on the advisory committees.

In the committee meeting yesterday we discussed at length how the state chairman might make contacts with the state health department. It was the consensus

in the committee that if the Children's Bureau would prepare a statement with respect to the Social Security Act, the committee would add to it suggestions for state chairmen. The committee felt that in this way the state chairmen might be given assistance as to how to approach the state health departments.

I hope, however, that the state chairman will in most cases go directly to the state health department or to the director of maternal and child health and ask about the plan.

Early in June the Children's Bureau is planning to hold a conference of the state directors of maternal and child health in Washington. We have already invited Dr. Grulee to attend this meeting to tell these state directors about the Academy and also Dr. Adair to discuss the work of the American Committee on Maternal Welfare.

DR. HILL .- I think a little note from you to the state health department would help a good deal.

DR. ELIOT.—When our field representatives can visit the states again that will be most helpful, as it has already proved to be.

DR. R. L. DeBUYS (New Orleans, La.).—May I ask Dr. Eliot what her interpretation is of the term "crippled child" in the federal statute? Does she interpret it as meaning the lame and the deformed which are orthopedic cases, or does she include the physically handicapped child who might be crippled from some other condition, and disabled, as for example, a cardiac case? I do not think the point she made about a child with a carious tooth being included as a crippled child is fair. It might be that he is potentially crippled, but he would not, in my opinion, because of the carious tooth, come under the term of a "crippled child."

DR. HILL.—In connection with the crippled child title, it has been ruled it is under the Board of Education.

DR. ELIOT.—I will answer Dr. Hill's question first with regard to the state agency that will administer the crippled children's program. The federal act simply states that it shall be administered by a state agency. The reason for this is that at the time the act was written there were five different types of state agencies administering programs for crippled children—state health departments, state departments of public welfare, state departments of education, commissions, and in one or two cases a state university hospital. In a few states more than one state agency appeared to have authority under the state law. The problem then was before the Children's Bureau as to which state agency should be designated. The matter was presented to the solicitor of the Department of Labor, who advised the bureau that it was a matter for the state and not the federal government to determine. In those states in which there was no state agency administering the crippled children's program, the procedure was left to the governor and the state's attorney general.

DR. DEBUYS.—That is the deformed child, the orthopedic case, but you can have a child who might be crippled from some other condition and be disabled like a child with a cardiac disease. I do not think the point you made about a carious tooth includes a crippled child. It might be potentially he is crippled, but he would not come under the term of the crippled child.

DR. ELIOT.—That again brings up the question whether the crippled child should be termed "handicapped." As to "disabled children" it is difficult to know exactly, Dr. DeBuys, what you mean. The orthopedically crippled child may be disabled or he may be ambulatory.

DR. EDGAR E. MARTMER.—May I ask Dr. Eliot if she will define cooperation as it applies to the health departments and the medical profession in the various states.

DR. ELIOT.—That is another point on which we have not laid down any definite rule. I think that is something for the medical profession and state health departments to work out. You would like to know what we have accepted up to the present time.

It was obvious that, for the first five-month period of operation of plans, the evidence of cooperation had to be largely in the form of plans. The Children's Bureau pointed out, however, in the latest information bulletin that has to do with next year's plans, that the plan must show evidence of actual cooperation, as, for example, conferences between the state health department and medical groups or meetings of advisory committees.

DR. MARTMER (DETROIT).—In Michigan we had arising the situation in which we had the health department calling a meeting at which the various groups were represented after the plan had been promulgated and after it had been accepted. Under these circumstances, there was little use in calling a meeting. After they have spent the money, what is the use of calling a meeting to discuss how it might have been spent?

DR. ELIOT.—Every year there is to be a new plan. I think that before these annual plans are actually submitted the medical groups might well go to the state health department to discuss the plans before they are sent in.

DR. MARTMER.—What would be the attitude of the Children's Bureau in regard to the statement requesting cooperation with respect to teaching, so far as the medical profession is concerned, as outlined in the report of the committee?

DR. ELIOT.—We are very much interested in this and are glad to see any state include an item in the budget which will further such educational programs. As you know, the Children's Bureau has done some work in this field, both in obstetrics and pediatrics. We will continue to assist when the states request it.

DR. MARTMER.—In Michigan the Academy members as a group put on a post-graduate program each year. The only criticism of the plan of the state health department was its educational features. Education was provided for every cooperating group except the medical profession. As the state health department program was submitted no provision was made for the education of the group (the general practitioners) who will have to carry this work on after the Social Security Act, as it now stands, is discontinued.

DR. ELIOT.—We are very much interested in having the medical groups come in to help us formulate plans for teaching.

DR. MARTMER.—We had provision made for teaching the public health officials, for teaching the lay groups and every group except the general practitioner, who, after all, is the backbone of the situation.

DR. ELIOT .- There is evidently something for you to do.

DR. STERLING H. ASHMUN (OIIIO).—I had supposed probably the same plan had been adopted in other states which we are fortunate to have in Ohio, as you well know. I think it might be interesting to other state chairmen to know the head of the state hygiene department is a member of the Academy. Dr. Van Horn, at the direction of the state health commissioner, directs nearly all of the present plans. Up to this time, he has placed four members of the Academy on his advisory committee. Being a member of the Academy himself, it looks to

me as though the cooperation in Ohio was pretty well insured. One thing he did which I thought was an excellent gesture and might be suggested to some of the other directors of hygiene or health or some of the others taking care of the work in a state was to write to the chairman of the state membership for the Academy to ascertain from the membership in the state what doctors were willing to help in any capacity in which they might be called upon.

Of course, that did not give me much idea of the capacity in which he might expect to call upon me. I wrote every member, and it was gratifying to have replies from over half the men in the state; some with very exclusive practices, some whom you would least suspect would volunteer their help, have come out whole-heartedly and have given assurance that in any capacity in which they can they will help to further this cause.

While in our state they plan to have an all-time man who is also a well-trained pediatrician, together with the nursing staff especially trained in maternity welfare departments; there will also be this other cooperation. If I am correctly informed, the plan as adopted in Ohio will certainly be a model for those who question what they mean by cooperation.

Our dental department is operating entirely separate from the medical and child welfare unit, and yet Dr. Van Horn, with the welfare unit, is making a special survey in Ohio of the pitted enamel teeth. How that is going to dovetail with the dental endeavor I do not know, but that certainly is a part of our department work. Although they expect to push their work into the counties where the needs are mostly rural, he expects to call on the men from the opposite end of the state so there will be no petty local jealousies, and they plan to pay them a satisfactory fee; at least that is the way it seems to most of those on the committee.

I might tell you that the advisory committee includes Dr. Gerstenberger, Dr. Horton, and Dr. A. Graeme Mitchell, heads of the department of pediatrics in three universities, and also me, as chairman of the state membership of the Academy. They plan to have these men go over the state With the facilities Dr. Van Horn has at his disposal to carry on, the proposed fee was twenty-five dollars a day and expenses. I do not think he would mind my mentioning that. While that might not represent what your efforts are worth, it is certainly better than men have been paid before for similar work. It looks to me as though this plan should work successfully.

The feebleminded child, which has been terribly neglected in Ohio, is not provided for in any of the set-ups so far. We have more children already committed by the probate courts of Ohio who are on waiting lists for care than could be provided for in two more institutions. If the crippled child happens to be a spastic with some cerebral deterioration, he is liable to be out. The department of crippled children cannot take care of a child mentally deficient, and it seems the Children's Bureau is going to have to correlate the work of a lot of departments.

DR. ELIOT.—This brings up a subject which is very important in the whole Social Security Act and also in title V, namely, qualifications of personnel. Under the federal act the selection of personnel, like tenure of office and compensation, is under the central of the state. The federal government, however, must determine whether there is "efficient operation of the plan" and qualifications of personnel have a good deal to do with efficient operation.

We discussed in our committee yesterday how the state chairman can help state health departments by supporting them in the choosing of qualified people to do this work. If the Academy and the pediatric sections of State Medical Societies did nothing else than to insist on good appointments, this would help enormously in the program.

The state and territorial health officers have adopted a statement with regard to qualifications of personnel which has been very helpful to the Children's Bureau.

Not only do the states have advisory committees, but the Children's Bureau has advisory committees appointed by the Secretary of Labor. These federal advisory committees have also helped by outlining qualifications for different types of personnel.

The chairman from Ohio did not mention the program in which the state health department is going to cooperate with the obstetric hospital association in making a study of maternal deaths in hospitals, a very interesting part of the Ohio program.

DR. ASHMUN.—I do not know whether it is well known among our membership, but it was rather a new idea to me that practically all of this work in which we will participate is educational only. There will be no money spent in treating children who have been neglected. There will be simple programs to bring the men in the various counties more up to date in their method of treatment and treatment will be left to them.

There seems to be a bit of doubt in the minds of many of our membership as to whether by cooperating in this way they might not be contributing to state medicine. That is always the fear back in their minds, but it seems to me if this is worked out on plans similar to Ohio's, it will be one of the finest factors for really uniting the whole medical unit in their own defense rather than making it in any way state medicine. All of this matter of treatment and immunization will be done absolutely by men in their own counties, not by men in other parts of the state.

DR. ELIOT.—The programs vary in different states with respect to this. There is no medical care of the sick in connection with the maternal and child health services. In certain states as part of their program, the state health departments may organize either child health conferences or other types of work that individual physicians in the rural communities may do in their offices, especially in communities where the population is scattered and where it is difficult to develop local services. That is one of the conditions in the federal act.

The state health departments organize conferences, prenatal or child health, the purpose of which is primarily educational. They are for those women who are not able for various reasons to take their children to their own private physicians.

The situations and needs in the various states are so different that obviously the plans must be different. The states are indeed working things out according to their own needs, and we are quite delighted with the fact there has been so much variation.

PRESIDENT DIETRICH.—Thank you very much, Dr. Eliot. I am sure you have helped to clear up many things about which we were in doubt.

The next order of business will be a report of the Committee on Hospitals by Dr. Munns.

#### Report of the Committee on Hospitals

DR. MUNNS.—Although the committee has done a great deal of work the last year, the report will be brief. We have completed and published reports on children's hospitals and pediatric sections of the general hospitals throughout the United States and Canada the past year. This year, we have cooperated with the Committee on Medical Education to prepare and publish a report giving detailed information concerning the house officer positions throughout the hospitals in this country and Canada. These positions include interneships, assistant residencies, and residencies in the various hospitals. At the present time the committee is

preparing a detailed report concerning the contagious disease hospitals in this country and Canada. The first section of this report has already been completed and is now in the hands of the publisher. The remainder of the report will appear in either two or three sections which will be published in later editions of the JOURNAL OF PEDIATRICS [volume 9, pp. 125, 377, 818 and volume 10, p. 136].

SECRETARY GRULEE.—I think, in connection with this report, it might be well to say in addition to this we found that the conditions throughout the country with regard to contagious disease hospitals are, to say the least, abhorrent. In most instances the so-called hospitals designated as contagious disease hospitals are nothing more than pest houses, with no status, no nursing facilities, nothing but a place to put somebody so he will not infect somebody else.

In the nature of things, it seems to me it is almost impossible to expect a small community to develop its own unit for care of contagious disease. The only way out of that is to educate the community to see that some portion of some hospital be set aside for such a purpose, and for that purpose the community as a whole should pay the expense. If that were done, operations such as for mastoiditis during scarlet fever could be assured fairly favorable conditions for their performance. I refer to the mastoid operation because in the Municipal Contagious Hospital, Chicago, a year ago last spring, there were eighty-six mastoid operations necessary following scarlet fever infection.

While that represents a group of about 500 cases a month over a period of six months, it still represents a considerable number of mastoid operations that were considered necessary by reputable men. What is a child in the small community to do under such circumstances? He cannot be taken to a hospital because they will not accept him in the hospital ward or in the operating rooms or in the private rooms. Some provision should be made for the child with contagious disease to be taken care of some place other than in the home in the small community.

That provision can be made, as I see it, only if certain portions of certain hospitals are set aside to take care of that need, and the public service, whatever it may be, municipal, county, or state, pay the cost. The condition is deplorable. I had no idea of what it was until we got into it. There are very few contagious disease hospitals in this country that are worthy of the name.

In a city like Chicago, there are only two places where a person with a contagious disease can be taken. In Cook County there is one other hospital where patients with contagious diseases can be taken. That represents a population of something like four million people, and the condition there is much better than it is in many parts of the country.

I was discussing the matter with the late Dr. Dennett and with Dr. Murray Bass. They said they knew of no place in New York where they could take a contagious disease case except the Willard Parker Hospital. That may or may not be true in New York, but that was the only place of which they knew. Something ought to be done for these children.

DR. MUNNS.—A great deal of what I have to say will appear in the report, but, since Dr. Grulee has mentioned it, I thought you might be interested in knowing the number of contagious disease hospitals found in the various regions of the Academy. In the Middle West, or Region III, there are just 26 contagious disease hospitals which can really be called contagious disease hospitals. In the Far West and South, Regions II and IV, there is a total of 23 contagious disease hospitals. In Region I, the East, there is a total of about 35 contagious disease hospitals, so you may see that the total number of contagious disease hospitals throughout the United States is not great. There are many other hospitals which are listed as contagious disease hospitals, but judging by the information given when the questionnaires were returned, it became quite obvious that they were really not contagious

disease hospitals. They were just separate buildings, possibly with one or two beds and a maid or so to take care of the building. There were no laboratory facilities or other equipment found in good contagious disease hospitals. In other words, they were just houses in which to put a patient who had a contagious disease and whom they did not wish to have near other people.

DR. ASHMUN.—Was there any follow-up on these? Was there any communication with the various hospitals, and did they get reports so they would benefit by these questionnaires?

SECRETARY GRULEE.—They will not have those yet because we have not compiled our report; we will probably put in a complete report, not modified but abridged, in the American Hospital Association Bulletin, where we have published all our reports heretofore, as well as in the JOURNAL OF PEDIATRICS. But really, Dr. Ashmun, that is not what meets the situation. Those hospitals are not hospitals, and in the smaller communities they are almost entirely politically controlled. They are a disgrace to the United States as a whole.

DR. ASHMUN.—I was thinking of the other element. In those which I visited there was considerable difference, for instance, in the infant and newborn death rates and in their maternal care, even in the most modern hospitals. Some of them have extremely high death rates. I wondered whether anything had been said to them calling their attention to that. They have superintendents appointed by politicians. I wondered whether the report would work to the good to which you intend to have it work.

SECRETARY GRULEE.—Of course, we can only do that by bringing pressure to bear from the medical profession, and perhaps the women's organizations in the state. If, for instance, we could call the attention of the League of Women Voters to the condition of contagious disease care in the United States we might be able to get some place. We have not considered that phase of it at all, because we have just arrived at the point where we are getting our statistics together.

Many of those hospitals, as Dr. Munns has said, have nobody to take care of patients except a maid. The only medical care they get is from some health officer. Something should be done about that situation. What we will do I do not know, but the reports will be available in the Bulletin eventually.

DR. MARTMER.—I am wondering, Dr. Grulee, if it would be of any benefit if a definition of what we consider a suitable institution could be drawn up and transmitted to the American Medical Association with the list of those hospitals that fall under that classification and perhaps along with that a list of those that do not, calling their attention to the matter. It this the proper method of approach to the American Hospital Association?

SECRETARY GRULEE.—The American Hospital Association would do more with it, I think. How much they would do I do not know. I believe the pressure will have to come from without as well as from within, not because of the hospitals themselves but because of their control which is essentially political.

DR. MARTMER.—If you could bring it first to the attention of the American Hospital Association and have it on record, then, taking it from the other angle, either to the Academy or to a state group of the Academy, would not this be the proper procedure?

SECRETARY GRULEE.—We can go to the American Hospital Association because we have access there, and they are very receptive. They are glad to get our material and have been very cooperative. I do not know what we had better do, but something should be done. It must be a campaign not of a year or two

years but of twenty years perhaps before we can get any place with it. It is not a problem which will be solved in a short time. Part of the difficulty is due to prejudice against contagious disease in hospitals on the part of laymen who feel that a contagious disease hospital is a sore spot in the community.

DR. MARTMER.—Is not that brought on, unfortunately, by the attitude of a large portion of the medical profession? For example, I am consultant in one of the hospitals. A patient develops crysipelas, and the hospital physicians immediately want to move the patient out of the hospital.

SECRETARY GRULEE.—Most hospitals will take care of contagious disease that develops within the hospital because they are afraid not to, but that is not the big problem.

PRESIDENT DIETRICH.—We will proceed to the next report, that of the Committee on School Health and School Health Education. Dr. LeRoy A. Wilkes is chairman.

DR. WILKES.—The Committee on School Health and School Health Education has submitted its report, which will be distributed. The one outstanding thing which impresses me continually, and the schools are only one example, is the failure of different community groups to state clearly their aims and particularly their scope of function. I think educational institutions have a tendency to get into medical practice; social agencies have the same tendency. In discussion in the New Jersey Social Conference this year, in which I happened to sit as a member, one of these agencies reported its next move was to form a health section. I asked what was to be the purpose of the health section in this conference, and the representative stated it was to take care of those medical cases that held back the social work in the community.

I asked whether they felt competent to take care of the medical phases, of the interfering factors that came up in social work. They said, "Yes we are, we will just get a doctor. The doctors are very kind to us so we will get them on our staff and refer the cases to them." I suggested it might be outside their proper scope of function; there was already a community agency founded primarily for that purpose, and I thought, if they would define their medical problems and submit them to the organization founded primarily for that purpose, the social workers would probably achieve their end more quickly and more completely than by attempting to insert in their organization a medical service section.

To their credit, I will say, they said, "Yes, we never thought of that." I think we might suggest to agencies founded for purposes other than health service, our readiness to help them, as a medical service agency, in the solution of their problems if they will stop trying to invade our field, will define their problems as they relate to medical service, and will request our cooperation.

I was very much surprised at the readiness with which the group in New Jersey seemed to realize that this was a better procedure and accepted it without question, and they immediately formed a health service section whose stated purpose and scope of function was merely to define the medical service problems which they encountered in their primary aim of social work and to present them to the proper community agencies.

If we would suggest to other groups that there is a proper scope of function for each community agency and that community agency services can never become integrated until each one understands what his peculiar and particular responsibility shall be, it would be the proper procedure. That applies to the schools and the social agencies of various types, and I think they are quite susceptible to the suggestion.

The remainder of the progress report of the Committee on School Health and School Health Education will be presented to you tomorrow in mimeographed form.

PRESIDENT DIETRICH.—Does the Committee on Medical Education have a report to make at this time?

DR. HELMHOLZ.—Mr. President, Dr. Veeder, the chairman of the committee, is not present. I have not the report well enough in mind to say anything more than that it deals entirely with graduate pediatric education and that, as was discussed, it seemed important that not only the matter of graduate education be studied, but also undergraduate education, as well as the giving of pediatric refresher courses to the general practitioner. It was our feeling that possibly it would be advisable to have one large committee consisting of three subcommittees to take care of these three distinct parts of medical education.

DR. M. HINES ROBERTS (GEORGIA).—As I sat in the meeting of the Committee on Child Health Relations yesterday, it occurred to me we would be extremely fortunate if many of the problems discussed there could be brought before the general meeting. It seems to me in the past few years fewer and fewer of these problems have been brought before the membership as a whole.

In the state of Georgia it has been very difficult for me to go back from these state chairmen meetings and put the problems over in the form in which we receive them in our committee meetings. It seems to me very worth while to consider devoting more of the time of our program to these public health problems rather than devoting the entire program to scientific problems.

PRESIDENT DIETRICH.—The Executive Board almost each year has tried to vary the program somewhat, and this subject is under discussion now. I would not be surprised if there would be a place on the program next year for discussion of that type.

SECRETARY GRULEE.—In other words, we plan to hold a longer meeting next year, probably a three-day meeting; perhaps half a day could be devoted to that purpose, with the entire membership present.

DR. CLIFFORD SWEET (CALIFORNIA).—I would like to make a short statement in regard to the JOURNAL OF PEDIATRICS. I have been discussing the matter with Dr. Veeder through correspondence this year: perhaps if I mention it here, some of you may think about it. I would like to see the JOURNAL OF PEDIATRICS have a department concerned with practical everyday things relative to the life of the child. I tested the matter out this year by inducing a friend from Oakland to submit an article on the mechanics of blowing the nose. It was promptly sent back from the JOURNAL OF PEDIATRICS because it was said to belong in a journal of the ear, nose, and throat. I asked Dr. Veeder whether it was not more practical to have this article appear in the JOURNAL OF PEDIATRICS where it would reach the people most concerned or whether it should appear in the Archives of Pediatrics where it would be brought to the attention of only a few people.

SECRETARY GRULEE,—I would like to speak on this from the other angle, that is the angle of the person editing the JOURNAL.

I wonder if any of you realize the amount of material which comes to a man who is editing the JOURNAL. I wonder if you realize how soon his journal would contain nothing but that material if it were presented in each issue. I do not believe the JOURNAL OF PEDIATRICS can afford to do what Dr. Sweet wants it to do unless it is done in the form of a supplement and done as an educational pamphlet in connection with the JOURNAL, subsidized from outside agencies. We have

committee reports; we have round table reports; we have panel discussion reports. We have reports of the national organizations, reports of the Executive Board, reports of the various regions, all of which are now published in our Journal. I think one of the most popular points of the Journal is its comprehensive reviews. If the Journal is to be of value, it must meet the demands of a varied group of individuals, and while it might meet the needs of this group in connection with some of these suggestions, it would not meet the wide needs.

Personally I think it would be far wiser to leave this matter in the hands of the editorial board in the first place; and in the second place, if we were to publish anything of that sort, it would be more advisable to provide some funds for a further increase in the size of the JOURNAL with that in mind rather than to ask them to take on that added burden. I speak feelingly because I have had this problem to confront for a good many years.

DR. SWEET.—I do not wish to be understood as criticizing the editorial board I feel there is great need for the presentation of the practical points which touch the lives of our children every day, in an authoritative manner to the people who can make use of them. I wonder how many pediatricians of this country are having children sent to the ophthalmologist outinely for study before the children enter school?

There are many thousands of children in the United States today blind in one eye because they did not learn the use of both eyes in childhood. A good many have been attempting to send their patients to the ophthalmologist at four, five, or six years in order to have a complete eye examination. That is not generally being done. I asked an ophthalmologist who writes well to send a paper on this subject to the Journal of Pediatrics, and again he received the reply this should be entered in a journal for ophthalmologists. The ophthalmologist does not see the child until he has difficulty with the eyes. We see the child and are in a position to find out whether or not he has difficulty.

I think these illustrations bring to your attention what I have in mind, that the Journal of Pediatrics should encourage the writing and publication of papers which concern the problems of the child in our everyday practice, insisting, of course, that these papers be well written, do not deal with controversial aspects of the subject in hand, and be presented in a clear manner so that the pediatrician and general practitioner everywhere will be instructed and the children of this country be greatly benefited.

SECRETARY GRULEE.—I do not question the advisability of the suggestions which have been presented. The only thing I question is whether it is up to us to do it under those circumstances and in that way.

PRESIDENT DIETRICH.—I think in connection with problems of this sort a great deal of good can be accomplished if they are presented at this particular meeting, because every state is represented here. Even if nothing can be done, it gives the members an opportunity to take home some new thoughts, to discuss them, and perhaps, if they are again presented to the Academy in the future, to do something with them. After all the Academy is still a very young organization. We have to change our plans from year to year and have to leave some things out and add other things. I think that ought to be borne in mind. We have progressed quite rapidly, but there is a limit in regard to what the Academy can do each year.

If there is nothing further to be brought before this body, I shall entertain a motion to adjourn.

Motion to adjourn was properly made, seconded, and carried, and the meeting adjourned at 10 r.m.

## REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

A REVIEW AND SUMMARY OF THE REPORTS ON CONTAGIOUS DISEASE
HOSPITALS IN THE UNITED STATES AND CANADA

Committee on Hospitals and Dispensaries: Dr. Clifford G. Grulee, Chairman; Dr. George F. Munns, Secretary; Dr. Murray H. Bass, Dr. Laurence R. DeBuys, Dr. Henry Dietrich, and Dr. Lewis Webb Hill.

The following is a résumé of the detailed accounts which appeared from time to time in the JOUENAL OF PEDIATRICS as reports from the Committee on Hospitals and Dispensaries of the American Academy of Pediatrics.

One hundred three hospitals received questionnaires from the committee. From among those returned, 88 were used to compile reports which have been published in current issues of the JOURNAL OF PEDIATRICS. Fifteen hospitals did not reply to the questionnaires in complete enough form to warrant their use, or the reply received indicated that they could hardly be classified as contagious disease hospitals. They were more of the nature of pesthouses.

South of the Ohio River and west of the Mississippi River there are few contagious disease hospitals. Only six questionnaires were received from the former region and only twenty-eight from the latter. Twelve of the twenty-eight were from California. There are several states in each region of the Academy of Pediatrics which do not have hospitals for the care of contagious diseases, and only two cities in all of the United States and Canada have more than one contagious disease hospital.

The attending staff, in most instances, is not a full-time one. Specialties are well represented on the attending staff of the hospitals, and among the larger institutions these men visit at regular intervals. Among the others they are, as a rule, only on call. Patients of many of the hospitals are not under the exclusive care of the attending staff. This means that their own physician may bring them to the hospital and care for them there, though he may not be a member of the staff.

Uniformly, these hospitals require the attending physician to have a doctor of medicine degree and be in good standing in his community. About two-thirds of the hospitals employ resident physicians and as a rule require them to have at least one year of previous hospital experience. There are a few that require only a doctor of medicine degree to qualify for that position. Generally, one thinks of a resident physician as an individual who has had at least one and preferably more years of previous hospital experience. We believe that at least one year of previous hospital experience is necessary to enable the average young physician to administer efficiently the duties of a resident. A contagious disease hospital which employs a physician whose only recommendation is a doctor of medicine degree and permits him to assume responsibilities that the title implies must certainly have a weak spot in the organization at that important point. There are, of course, certain small hospitals which at some period during the year have very few or no patients. This situation would make it extremely difficult for them to secure a man of previous experience, for he would not care to waste his time where patients are few but would seek experience in the larger institutions with active year-round services. About one out of five hospitals employs an assistant resident, and in most instances at least one year of previous hospital experience is required in order to qualify for this

position. Slightly less than half of the hospitule employ internes, and in most instances previous hospital experience is not required. Generally, the length of the service is less than six months.

The committee is of the opinion that information concerning house officer positions reveals a rather serious weakness in the training of the average young physician for the practice of general medicine. A thorough knowledge of contagious diseases is an extremely valuable asset to the general practitioner and, as far as that goes, to any other practicing physician. Judging by the number of house officer positions available in contagious disease hospitals, we are led to conclude that many men probably complete their hospital training without adequate contagious disease training and possibly some of them without having ever seen more than very few cases of contagious disease.

Slightly more than one-third of the hospitals (25) are connected with medical schools and among a slightly larger number, the clinics or ward rounds are available to medical students. In general, it might be said that the hospitals which are connected with medical schools usually have a superior organization and equipment. Fewer than one-half of the hospitals have observation wards or cubicles or private rooms which might be used for observation purposes. Among those hospitals having these facilities, new patients are usually retained there until a positive diagnosis is made. It would seem that some form of isolation unit is essential to any contagious disease hospital, and, when our figures indicate that more than 50 per cent of them do not have this type of unit, we wonder if perhaps our questions were not clearly understood.

Slightly more than two-thirds of the hospitals take routine throat cultures for diphtheria on admission. Fewer than one-half take them for hemolytic streptococcus, and fewer than one-third take routine vaginal smears. Routine blood counts are done in fewer than one-half of these institutions, and four-fifths of these hospitals take routine urinalyses on admission. Among nine-tenths of them routine histories and physical examinations are done. Information was also secured concerning routine procedures such as Dick, Schick, von Pirquet, Mantoux, and Wassermann tests. Most of the hospitals perform this latter group of tests only when indicated. There were a few in which they were routinely performed. We believe that the routine procedure of contagious disease hospitals where patients are placed in wards, and particularly is this true among children, should at least include throat cultures, blood counts, urinalysis, and vaginal smears and complete history and physical examination. Too many of the hospitals which replied to this questionnaire omitted one or more of these procedures.

About two-thirds of the hospitals are located in rather quiet residential districts; the remainder are located in noisy, rather undesirable locations. Slightly less than two-thirds of the hospitals are small institutions, each having only one or two floors. Slightly over one-third of the entire number have bed capacities of fifty or less; about the same proportion have one hundred or more beds; and a similar number have a bed capacity between fifty and one hundred. Thus, about two-thirds of all the hospitals have fewer than one hundred beds and hence cannot be classified as large institutions. These figures should be kept in mind as additional information concerning various departments of these hospitals is revealed. Most of the hospitals have wards and about two-fifths of them have all or part of their floor capacity in a cubicle system.

Among all hospitals there were 4,696 ward beds. Hospitals found in Regions I and III supplied more than four-fifths of the total number. About three-fifths of the hospitals accept all types of contagious diseases. Some exclude certain types, usually such as crysipelas, measles, chickenpox, pertussis, gonorrhea, and syphilis. Surprisingly, two exclude diphtheria, and several exclude typhoid fever. Among the larger hospitals which usually have greater facilities for isolation of patients, ex-

clusion of certain types of contagious disease is usually unnecessary. However, the smaller institutions may have less space for individual isolation; their nursing facilities are more limited; and it is probably imperative for them to exclude certain types of disease in order to protect other patients.

Figures on the total admissions to these hospitals reveal only twelve institutions in the entire group which had admissions of 5,000 or more patients in any one or more of three years, 1932, 1933, and 1934. Exactly two-thirds of the hospitals did not admit over 1,000 patients in any one of the three years. The percentage of deaths in hospitals of Regions II, III, and IV is about the same for the three years, 1932, 1933, and 1934, but was almost one-third lower than among the hospitals of Region I. In fact, during one year, 1933, the percentage was two-thirds less. We are unable to account for this marked difference in death rate.

Practically all hospitals accept both white and colored children. In Region II all are segregated; among the hospitals of the other three regions, twenty-five segregate white and negro patients. No hospital limits the number of negroes who may be admitted. There were at least twelve hospitals in which all beds are charity beds, but we did not hear from all the institutions in regard to this question. A large number have from 50 to 90 per cent charity beds, and probably less than 2 per cent of the institutions have all strictly pay beds. Only thirteen hospitals provide accommodations for mothers to stay with their sick children. Most of the hospitals in every region are supported entirely by county and city funds. Only one institution reported that it is aided by state funds, and no hospital derives its entire support from endowment. There are a few which are partially supported in that way. Only two hospitals receive aid from the community chest, but four are entirely supported by private contributions.

The cost per patient per day revealed interesting variations. The lowest figure reported was \$1.82 and the highest \$6.53. This rather marked difference in cost can be interpreted as you please. A low figure may suggest inefficiency, inadequate equipment, and poor care and food. On the other hand, a high figure may also mean inefficiency and needless waste with no better food, care, or equipment. Our attempt to obtain detailed information concerning supplies, food costs, nursing costs, etc., was in most instances unsuccessful. Among the few replies received, there was again a great difference in figures.

About three-fifths of the hospitals employ men superintendents; the remainder employ women. About one-half of the superintendents are physicians; one-fourth are registered nurses; and the remainder are lay people. Many of these officers are probably well trained and capable, but the committee wishes to emphasize a point made in an earlier report. We believe that the position of superintendent of any hospital, particularly a large hospital, requires a thorough preliminary training in hospital administration and that the mere possession of a doctor of medicine or registered nurse degree together with a smattering of practical experience is not in itself a complete qualification for that position.

The nursing organization of many hospitals seems to be excellent but among a few appears to be decidedly inadequate. About two-fifths of the hospitals are affiliated with other hospitals for special training of nurses. A somewhat larger number offer courses in contagious nursing technic. These courses vary in length of time from three weeks to three years. The average affiliate course is about three months. We doubt that any period of less than three months' training could be of very much value. One-half of the hospitals employ only graduate nurses. About two-thirds of the hospitals immunize the nurses to diphtheria and about the same number vaccinate them against smallpox. Fewer than one-half immunize to scarlet fever, and about one-third immunize to typhoid fever. Nurses contracted diphtheria in only ten hospitals and scarlet fever in only twelve. Only one nurse in all of the hospitals contracted smallpox. Among about one-fourth of the hospitals nurses

contracted other contagious diseases such as mumps, measles, poliomyelitis, etc. Among most of the hospitals the total number of nurses who contracted one of the contagious diseases was small. A larger number had scarlet fever. In those instances in which immunization is possible, it is a most sensible routine procedure when applied to individuals in constant close contact with contagious disease. We believe that all contagious disease hospitals should afford their nurses that protection.

The information which we received concerning the number of nurses on day and night duty, the length of their assignments, etc., was generally unsatisfactory, probably because of a misunderstanding of the questions asked. We are unable to give accurate figures concerning this information. In general, most of the hospitals seem to have an adequate number of nurses on duty at any one time. In a few institutions the nursing care seemed to be decidedly inadequate both day and night. As a rule, among those replying, a graduate nurse is found in charge of the wards both day and night, but many did not reply to this question, which makes us wonder whether ward supervision in many hospitals is what it should be.

Figures on cross-infection, too, are not as instructive as they should be, as many hospitals failed to reply to this portion of the questionnaire. However, what information we have indicates that these infections are not uncommon. Measles and scarlet fever were the most frequent offenders. Chickenpox was also a common offender. Diphtheria as a cross-infection was infrequent. It occurred seven times in fifty-three hospitals, and three of these cases occurred in one hospital. Measles and varicella were the only diseases that occurred frequently as a cross-infection in any hospital. Several institutions reported as high as forty or more cross-infections with these diseases within a year.

Two-thirds of the hospitals have a special operating room. Relatively few operations are performed in contagious disease hospitals, but one is curious to know what happens when it is necessary to operate upon a patient in any of the hospitals (about 30) which have no operating room.

Comparatively few of the hospitals have special kitchens for the preparation of infants' and children's diets. Some of the larger hospitals have them, but they are usually lacking in moderate-sized or small hospitals. In these small institutions, a special diet kitchen may not be practical or necessary. However, any hospital having a fair-sized, active service with children and babies frequently among the patients should have a special kitchen for the preparation of their food. Our information indicates that diets for both children and adults are not well handled in several of the hospitals.

#### X-RAY SERVICES AND LABORATORIES

Fewer than one-third of the hospitals have no facilities for x-ray work. This means that neither have they a department of their own nor is a department in another institution available. In the larger institutions complete x-ray service is usually available. In the smaller institutions often it is available for diagnostic purposes only. Among those institutions which are part of a large general hospital, the x-ray department of that hospital usually serves the contagious disease division. The x-ray may not be used relatively as frequently in contagious disease work as it is in general medicine, but one can think of many instances in which its aid is a decided advantage, and often the information which it may give is essential. Therefore, when we find that about 33 per cent of contagious disease hospitals in this country have no facilities for x-ray work, we believe that another marked weakness has been revealed.

Nearly one-third of the hospitals employ a full-time director of laboratories. This position includes supervision of pathologic, clinical, bacteriologic, and serologic laboratories. About two-thirds of them employ either a full-time or a part-time

director. Laboratory work in about one-third of the hospitals is done by the city or state health departments or by the laboratory of another hospital. More than one-third of the hospitals have a full-time director of the pathologic department, and about two-thirds of them have either a full-time or part-time director. In many instances, these men are also the directors of the laboratories of a general hospital of which the contagious disease hospital is a division and, of course, the laboratory work of the contagious disease hospital is done in the laboratories of the general hospital.

The percentage of autopsies for all hospitals is a little better than 50. Among the larger institutions this percentage will average much higher than this figure, but several of the smaller hospitals which report few or no autopsies pull the general average down considerably.

Slightly less than one-half of the hospitals have full-time directors of the clinical laboratory, and slightly more than one-half have either a full-time or part-time director. More than one-half of the hospitals employ full-time technicians in the clinical laboratory and among slightly less than one-half the interne performs part of the routine work.

Many institutions have well-equipped laboratories, including facilities for blood chemistry work, basal metabolism tests, etc. About two-fifths of them have facilities for research work. All institutions did not reply to this question, but of those who did, about 10 per cent considered their clinical laboratory facilities inadequate. About two-fifths of the hospitals have full-time directors of the bacteriologic laboratory, and two-thirds have either full-time or part-time directors. In about one-third the interne performs some of the laboratory work, usually of a routine nature. More than one-half of the hospitals employ full-time technicians and more than one-half keep animals for experimental purposes. About one-half have facilities for research work; again, more than 10 per cent considered their laboratory facilities inadequate. About two-fifths of the hospitals have full-time directors of the serologic laboratories. Almost one-half have either full-time or part-time directors, and one half have full- or part-time technicians. The internes have duties in the serologic laboratory in only ten hospitals. About two-fifths of the hospitals perform their own Wassermann tests, and the same number are equipped for research work. Again, about 10 per cent or more consider that their laboratory facilities are inadequate. About two-fifths of the hospitals have facilities for photography, and almost onehalf have an electrocardiograph available.

In general, one might conclude that laboratory work done in many of the hospitals is not very complete, and, judging from information from the laboratories alone, we might say in many instances this work is inadequate. However, we must not lose sight of the fact that many of the institutions concerned in this report are small and that for them complete laboratory organization with full-time technicians would be a prohibitive expense. In most instances, these smaller hospitals have access to the laboratory of a large institution or to the laboratories of the department of health in their respective city or county. We are sure that in about 10 per cent of the hospitals the laboratory facilities are inadequate, for at least that number so replied to that section of the questionnaire.

Trained dictitians are in charge of the dict kitchens in about one-half of the hospitals. Most of these dictitians seem to have had adequate training, while a few have not. In some institutions the patients' food requirements are left to the tender mercies of a cook or maid. At first sight this does not seem to be a very satisfactory arrangement, although there are some cooks to whom we would rather trust the gastronomic peculiarities of our patients than to the cold logic of standard dicts.

In about one-third of the hospitals, standard special diets are drawn up by the attending physician alone. In about one-fourth the physician and dietitian cooperate,

and in more than one-fourth the dietitian alone arranges the diet. In general, the diets seem to be well supervised. The larger hospitals all employ trained dietitians, and we suppose that among the smaller institutions they cannot afford to pay special dietitians unless their work is combined with other duties.

About two-fifths of the hospitals maintain a social service department or are served by the social service department of a large general hospital. Almost all of these departments have a full-time worker in charge, who in most instances, with the exception of two or three, has had special social service training. Many of the larger hospitals have more than one full-time worker. About two-fifths of the hospitals investigate all patients who are admitted. In two-thirds of them this work includes home visits. The remainder gain their information solely through contact with patients and relatives who visit the patient in the hospital. Slightly less than one-third of the hospitals take complete social histories, and almost three-fourths of them file the social history with the medical history. Among the remainder an abstract is usually filed. About one-third of the hospitals investigate the ability of the patient to pay for hospital services.

Less than one-fourth of the hospitals have available convalescent homes, and about the same number have foster homes. Many of the hospitals consider their facilities for convalescent care inadequate, particularly in the case of children. This complaint is made not only by hospitals who have no facilities for convalescent care, but often by those who report that they have access to such facilities. In general, we are forced to conclude that facilities for convalescent care among contagious disease hospitals need considerable improvement and enlargement.

Slightly more than one-fourth of the hospitals routinely follow up discharged patients. Usually the social service department does this work. Very few of the hospitals use volunteer workers. Most of the social service departments are supported by hospital funds, although there are eight departments in Region I which are supported by outside funds. In very few hospitals is there a lay committee in charge of the social service department. Physicians are members of this committee in three instances. Lay committees may be valuable aids to the social service departments, but certainly no such committee is qualified to direct activities of that department, even if the committee includes a physician or two.

During 1934 these hospitals cared for 4,462 cases of diphtheria. The average mortality was 7.2 per cent. These figures indicate that much remains to be accomplished in the campaign for eradication of diphtheria. In the same year 26,246 cases of scarlet fever were admitted to these hospitals, a number larger than all other contagious diseases admitted to the hospitals combined. The average mortality was 1.45 per cent. With increasing use of preventive measures, one should expect to see the first figure considerably lower during the next few years and with more widespread and intelligent use of new forms of treatment, we should also expect to lower the mortality rate. Proper use of convalescent serum and the Dick serum gives us two fairly effective weapons of combating this disease. There were 5,917 cases of measles admitted to these hospitals in 1934. Region III seemed to suffer an unusually violent type for their mortality rate was twice that of Region I and more than six times that of Regions II and IV. The rates respectively are 6.3 per cent, 3.1 per cent, and 0.96 per cent. About the same number of cases of pertussis as of measles were cared for in these hospitals. The average mortality was 7.9 per cent, provided that the figure for one hospital is not included. This particular institution in Region IV reported 1,824 cases of pertussis in 1934 with the remarkably low mortality rate of 1.07 per cent. The mortality figure of 7.9 per cent should emphasize once again that pertussis is one of the most dangerous of the contagious discases. A factor in this situation, however, must be that usually only cases of this disease with complications are hospitalized. Smallpox, against which we have waged a campaign for many years, caused only one death among a total of two hundred

and fifty-six cases admitted to these hospitals. In Region I only one case was admitted among all the hospitals, and it was a fatal case. That figure speaks well for preventive work in that region. Region III cannot be so proud of their record with fifty-six cases reported. In Region II, only four cases were reported, but in Region IV, one hundred and ninety-seven cases were reported with about seven-tenths of these being reported from one hospital (17). Among 4,824 cases of chickenpox the mortality rate averaged 0.3 per cent. Among 383 cases of epidemic cerebrospinal meningitis, the mortality was 43.9 per cent, a rather discouraging figure indeed, but probably destined to be lower in the future when recently improved methods of treatment are more widely used.

Figures on other contagious diseases reflect outbreaks of various epidemics in different parts of the country, such as the amebic dysentery epidemics in Illinois, the encephalitis epidemic in Missouri, and typhoid fever outbreaks in several cities. More detailed information on these epidemics is given in previously published reports.

#### SUMMARY AND SUGGESTIONS

It is readily seen from this review that the contagious disease hospitals of the United States and Canada are far from being what they should be. There is perhaps some excuse for the lack of x-ray facilities in so many, but this can certainly not be urged for the inadequacy of their laboratory facilities. These criticisms hold true for many of even the larger hospitals. It would seem that under the circumstances some other provision for the care of contagious disease cases should be made than is at present available.

Would it not be better in smaller communities for the contagious cases to be taken care of in connection with some well-recognized hospital where general facilities on the care of sick patients are available? This could be done by most communities without any increase in cost and would certainly result in better treatment of the patients. This does not visualize the necessity of including these cases on a floor of the hospital, but there should be some definite physical connection, and certainly, if it did nothing more, it would make available nursing care and medical attention which is not readily attainable in most instances.

It should be borne in mind that this survey covers a comparatively few of the hospitals which are designated contagious disease hospitals. As a matter of fact, most of the smaller ones which have been eliminated are used simply as places to put patients with contagious diseases so that there will not be a danger to the community, but without any, or at best inadequate, care for the patient himself.

This report completes the review of contagious disease hospitals.

The committee takes this opportunity to thank all persons in this country and Canada who so kindly took the trouble to see that the questionnaires were filled out and returned to us.

#### News and Notes

The American Board of Pediatrics reports the results of three examinations held in October and November.

On October 22, in San Francisco, 19 men were examined. Ten were passed, and 9 failed. Of the number passing, one was in Group I, 5 in Group II, and 4 in Group III. Of the number who failed, 3 were in Group I, one in Group II, and 5 in Group III. Figured on a percentage basis 52+ per cent passed and 48- per cent failed.

On November 15, in Baltimore, 34 men were examined. Twenty-five were passed, and 9 failed. Of the number who passed, 2 were in Group I, 10 in Group II, and 13 in Group III. Of the number who failed, 2 were in Group I, 5 in Group II, and 2 in Group III. The percentage on this examination shows 73.5 per cent passed and 26.5 per cent failed.

On November 19, in Cincinnati, 32 men were examined. Twenty-six passed, and 6 failed. Of the number who passed, 3 were in Group I, 6 in Group II, and 17 in Group III. Of the number who failed, 2 were in Group I, one in Group III, and 3 in Group III.

Grouping these three examinations together, 85 were examined: 61, or 71.8 per cent, passed and 24, or 28.2 per cent, failed. Of the number who passed, 6 were in Group I, 21 in Group II, and 34 in Group III. Of the number who failed, 7 were in Group I, 12 in Group II, and 10 in Group III.

The following men and women have been certified by the American Board of Pediatrics since the last report. Fifty-one of these men and women were examined.

Jessie M. Bierman, Helena, Mont.
Kenneth Blanchard, East Orange, N. J.
George E. Brockway, Brooklyn, N. Y.
Leon H. Dembo, Cleveland, Ohio
Banice Feinberg, Providence, R. I.
Sandor A. Levinsohn, Paterson, N. J.
Harry A. Ong, Washington, D. C.
Edward Warren Ripley, Montelair, N. J.
W. Russell Smith, New York, N. Y.
J. Hart Toland, Philadelphia, Pa.
Frederick H. von Hofe, East Orange,
N. J.
James Robert Adams, Charlotte, N. C.
William Staton Anderson, Washington.

D. C.

John Edmund Ashby, Dallas, Texas
Leo Batell, Forest Hills, N. Y.
Allan Penny Bloxsom, Houston, Texas
Maxwell Bogin, Bridgeport, Conn.
Carl C. Fischer, Philadelphia, Pa.
Kenneth B. Geddie, High Point, N. C.
Thomas Archer Gibson, Winchester, Va.
Ernest Foster Gordon, New Haven, Conn.
Algie S. Hurt, Jr., Richmond, Va.
Arthur Hill London, Jr., Durham, N. C.
Irving Matusoff, Brooklyn, N. Y.
Francis Charles McDonald, Boston, Mass.
Robert Carey McGahee, Augusta, Ga.
Rhoda May Mickey, Valhalla, N. Y.
Philip A. Mulherin, Augusta, Ga.

Julian P. Price, Thorence, S. C.Donald Edward Robinson, Burlington,N. C.

Allan Roos, New York, N. Y.

John M. Saunder-, Nashville, Tenn
Suzanne Schaefer, New Orleans, La.

Samuel Singer, Philadelphia, Pa.
Reuben Turner, New York, N. Y.
Robert O. Y. Warren, Wilmington, Del.
James Henry Bahrenburg, Canton, Ohio
Samuel Sidney Bernstein, Detroit, Mich
William W. Briant, Jr., Pittsburgh, Pa
Merlin L. Cooper, Cincinnati, Ohio
Robert J. Cooper, Pontiac, Mich.
Max Deutch, St. Louis, Mo
Jerome Diamond, St. Louis, Mo
Jerome Diamond, St. Louis, Mo.
Samuel D. Edelman, Columbus, Ohio
Ernest Ekermeyer, Nenia, Ohio

Arthur J. Horesh. Cleveland, Ohio
Irvin R. Itkoff, Cincinnati, Ohio
Rockwell M. Kempton, Saginaw, Mich.
Harry C. Kendall, Cincinnati, Ohio
Carl A. Koch, Cincinnati, Ohio
Daniel B. Landau, Hannibal, Mo
Waldo E. Nelson, Cincinnati, Ohio
William Woodward Nicholson, Louisville,
Ky.

Carl J. Ochs, Cincinnati, Ohio Margaret Knight Patterson, Detroit, Mich.

Louise W. Rauh, Cincinnati, Ohio

Clare R. Rittershofer, Cincinnati, Ohio Charles Lee Shafer, Mansfield, Ohio Aaion Allen Shaper, Louisville, Ky. Inman Smith, Trion, Ga. J. Gay Van Dermark, Covington, Ky.

Maurice Bernard Weiner, Detroit, Mich.

Following the action taken by the assembly of the official delegates of the thirty eight governments attending the first congress in Paris in 1933, the Second International Congress for the Protection of Infancy will be held in Rome.

The date, approved by the Italian government, is fixed for the days October 4 to 8, 1937, immediately after the Fourth International Pediatric Congress which will take place also in Rome, September 27 to 30, 1937, at the time of the bimil lenarian celebration of the Emperor Caesar Augustus

The official languages are English, I'rench, German, Italian, and Spanish.

Admission to the Congress is open to all those who in the field of their respective activity take an interest in the multiform problems of the protection and assistance of infancy: doctors (pediatrists, obstetricians, hygienists), jurists, pedagogues, and administrators of works of assistance.

The subscription rate is 100 Italian lire. Those who wish the Transactions of the Congress should add 50 Italian lire. The fee must be sent to the treasurer of the committee Dr. Egidi, Corso Bramante 29, Torino 120.

The program of the Congress, with the dates of the inauguration, scientific meetings, visits, receptions, will be sent afterward to all subscribers

For information concerning travel, railway rates, and reductions and for various facilities of sojourn (hotels, gasoline, etc.) foreign visitors should communicate with the bureaus of the Italian Company of Tourism (C.I.T.) in the different countries

For general correspondence and for the first section address Prof. G. B. Allaria, President of the Organizing Committee, Corso Bramante 29, Torino 120. For correspondence of the second section address Dr. Paolo Gaetano, member of the organizing committee for the second section (via Angelo Brofferio 9, Roma).

#### Organizing Committee

- Prof. Giovanni Battista Allaria—Director of the Pediatric Institute of the Royal University of Turin, president of the Italian Pediatric Society; president.
- Or. Paolo Gaetano—S. Attorney General of the Supreme Court of the Kingdom of Italy, vice president committed of the Italian Union of assistance to infancy (Section of the "Union Internationale de secours aux enfants" de Geneve), vice president.
- Prof. Nicola Pende—Director of the Institute of Medical Pathology of the University of Rome, Senator of the Kingdom.
- Prof. Francesco Valagussa—Director of the "Preventorio Maraini" in Rome, Senator of the Kingdom.

Directions Concerning the Reports, the Communications, and the Discussions

1. Subjects of reports.

#### First section-hygienic and sanitary aspects

- 1. Preventive measures against infant mortality from diseases of nutrition;
- 2. The institution of climatic colonies for children;
- 3. The sanitary assistance to children of Europeans in colonial countries:
- 4. The physical training for school children;
- 5. Preventive measures against the sanitary inferiority of illegitimate children.

#### Second section-juridical and social aspects

- 1. The social foresight in reference to minors and the international agreements;
- 2. The destiny of sons in the case of annulment or dissolution of marriage, from the juridical and social point of view;
- 3. In what manner the legislator can intervene for carrying into execution the principles of the statement of Geneva?
- 4. The juridical protection of minors in international relations;
- 5. The obligatory assistance to the mother and to illegitimate children.

The maximum space at the disposal of authors in the Transactions of the Congress will be the following:

For each relator-5,000 words,

For each correlator-1,500 words,

For each individual communication-700 words,

For each speaker who intervenes in the discussions-350 words.

Final dates for arranging for places on the program-May 30, 1937.

The American Board of Pediatrics will hold an examination in New York City on Jan. 23, 1937, and another in Atlantic City on Sunday, June 6, 1937. This latter date comes between the meeting of the Academy and the meeting of the American Medical Association. Further information in regard to appointments for examination may be obtained from the secretary, Dr. C. A. Aldrich, Winnetka, Ill.

Dr. Arthur Stern, the organizer of the first milk dispensary and baby welfare stations in New Jersey, died November 28, 1936. Dr. Stern was born in Germany in 1868 and settled in Elizabeth, N. J., in 1892. He had specialized in pediatrics since 1911 and was Chief of the Pediatric Department of the Elizabeth General Hospital, St. Elizabeth's Hospital, and Alexian Brothers' Hospital, of Elizabeth, N. J., besides being consulting physician to the Rahway Hospital of Rahway, N. J.

Besides his membership in the American Academy of Pediatrics, Dr. Stern was a Fellow of the American College of Physicians, Fellow of the Union Internationale de Secours aux Enfants, and formerly Commissioner of Health of the City of Elizabeth. Dr. Stern was of a kindly nature and intensely interested in the welfare of children; he was one of the pioneers in pediatric work in the state of New Jersey.



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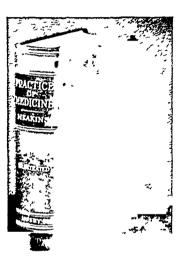
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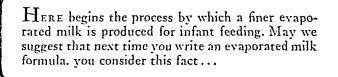
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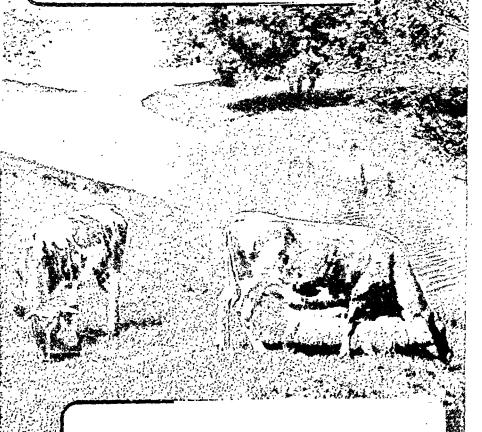
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In Hillard W Willis M.D., Louisville, Ky.

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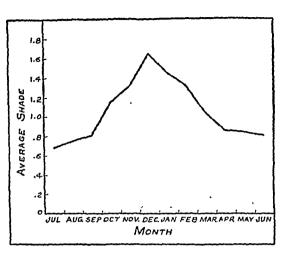
By Sumuel Karchitz M.D. Charles K. Greenwald and A.J. Klein, New York N. Y.

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## WEATHER FORECAST-

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It is probable that conditions are similar in many smaller cities especially where soft coal is used and wind velocity is low.

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Atmospheric pollution is but one of many forces militating against the therapeutic effects of ultraviolet rays in winter. Others, to name only a few, are cloudiness, precipitation, and clothing. In winter, moreover, it is often impracticable to give sunbaths to infants during the very time they are most susceptible to rickets—the first six months of life.

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But the defensive mechanisms of the body capable of preventing changes in reaction may be deranged in disease with consequent acidosis or alkalosis. Acidosis is associated with hyperpnea, diarrhea, dehydration, anoxemia, circulatory or renal insufficiency; alkalosis with excessive breathing, vomiting.

Treatment of acidosis is designed primarily to correct the underlying cause. In most types, fluids and fruit juices with Karo are forced every hour. In cases associated with ketosis (except where it is a disturbance in carbohydrate metabolism, as in diabetes mellitus) 20% dextrose is given intravenously at repeated intervals. In case of diabetes, insulin is given, by some authorities, simultaneously one unit for each gram of dextrose, until the condition is controlled.

CAUSES	OF ACIDOSIS								
EXCESSIVE ACID FORMATION									
Acid	Disturbance								
	Starvation								
Aceto-acetic	Cyclic vomiting								
B-hydroxybutyric	Diabetes								
	Ketogenie diet								
	Asphyxia								
	Intestinal intoxication								
Lactic	Respiratory failure								
	Shock								
	Burns								
DEFECTIV	E ELIMINATION								
Metabolite	Disease								
Phosphate	Nephritis								

Carbonic scid

Emphysema

Narcosis

Respiratory obstruction

Myocardial failure

CAUSES	OF ALKALOSIS
EXCESSIV	E LOSS OF ACID
	Hyperventilation
	Tetany
CO 2	Cerebral lesions (respiratory center)
	Hysteria
	Excessive crying
	Vomiting
HC1	Pyloric stenosis
	Intestinal obstruction
EXCESSIVE 1	NTAKE OF ALKALI
NaHCO 3	in Pyclitis
	in Nephritis

From Kugelmass' "Clinical Nutrition in Infancy and Childhood" - (Lippincott)

Treatment of alkalosis depends upon the cause. The most common variety in children is that resulting from prolonged vomiting with loss of acid, salt and body water. No food is given by mouth except fluids with Karo, and saline intravenously. If alkalosis is the result of alkali administration in the presence of nephritis with poor kidney excretion of salts, large amounts of fluids with Karo will favor excess base elimination. Alkalosis from excess alkali administration is alleviated by forcing fluids with Karo.

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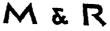
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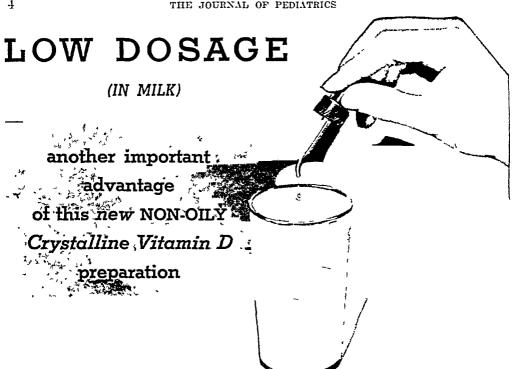
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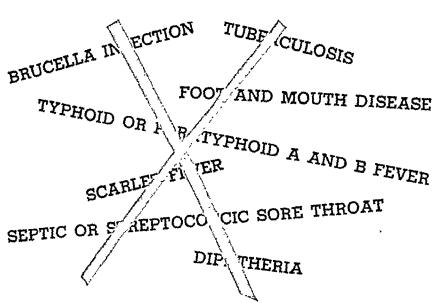
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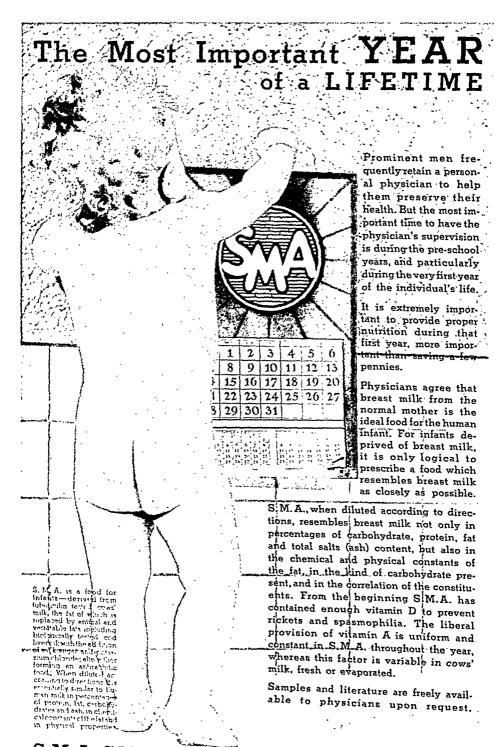
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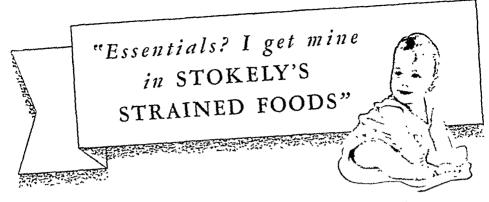


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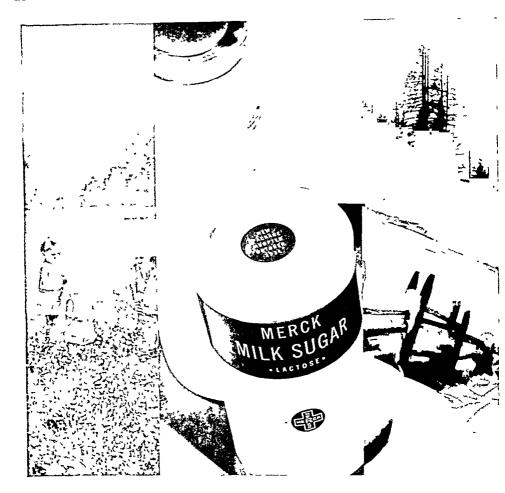
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Friedman, Samuel, Infant feeding and nutrition a decade of progress, 1m J Dis Child 19 153-190, January '35

<sup>\*\*</sup>Barenberg, Louis II., and Abramson, Harold, The effect of large amounts of mill sugar on the stocks and nutrition of infants, Arch, Pediat 17 1, January '30

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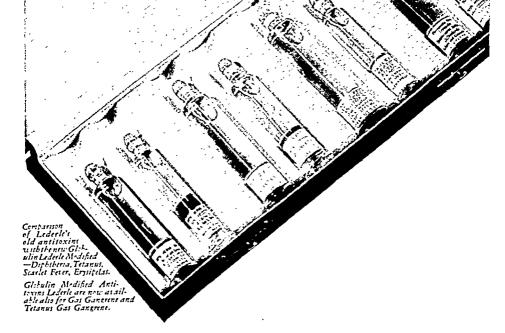
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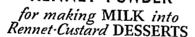
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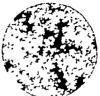
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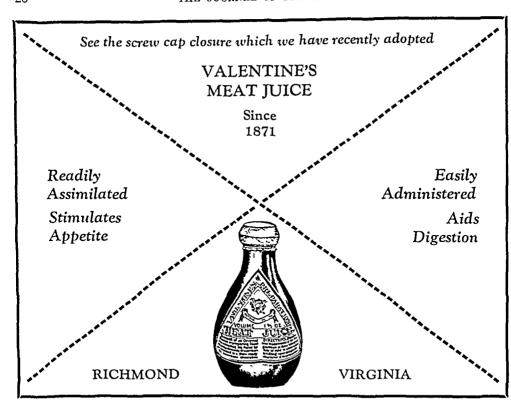
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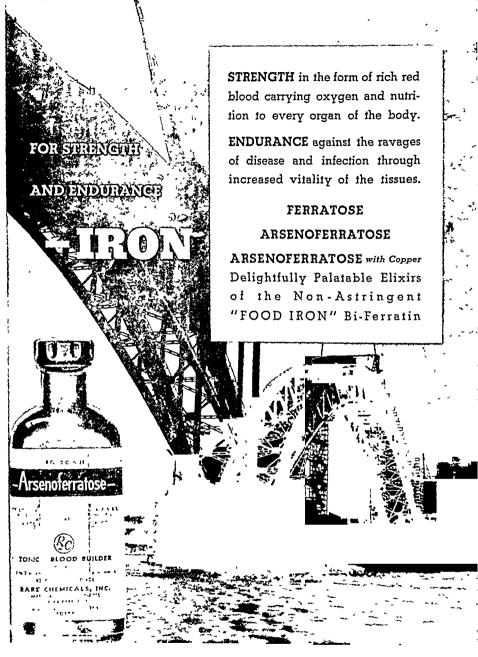
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## The Journal of Pediatrics

NOVEMBER, 1936

Vol. 9

No. 5

### Original Communications

### CONGENITAL SYPHILIS

IN THE LIGHT OF THIRTY YEARS' INVESTIGATION OF THE SPIROCHETE AND TWENTY-FIVE YEARS' EXPERIENCE WITH SALVARSAN

Erich Hoffmann,† Bonn, Germany Translated by H. A. Haynes, Jr., M.D., Ann Arbor, Mich.

#### FOREWORD

I T WAS for three reasons that I decided to publish my lectures given in Santander on the problem of congenital syphilis. First, much confusion and misunderstanding remained in spite of Matzenauer's advances (1903) and the definite results of etiologic investigations in Germany since 1905. Newly acquired facts made a new presentation desirable, especially as they can be vouched for from personal experience.

Second, I wished to present the results of German research in other countries for the information of physicians and to clear up misunderstandings which are still hindering the battle against this world epidemic.

And third, I am convinced that today this subject demands closer cooperation between pediatricians, syphilologists, gynecologists, pathologists, and those engaged in other branches of medicine. However, in the successful struggle for the freeing of humanity from the scourge of syphilis, it is especially important to prevent the transmission of the disease, falsely called hereditary syphilis, and thereby free innocent children from the curse of a generalized infection with which they become afflicted even before birth. May this goal soon be reached by every friend of humanity, and may further useful contributions follow this unified presentation. Then, indeed, the elimination of syphilis will no longer be pointed to as Utopian.

Bonn, December 31, 1935.

ERICH HOLFMANN.

<sup>\*</sup>Die Angeborene Syphilis im Lichte 30 jahriger Spirochaten-un 25 jahriger Salvarsanforschung Abhandlungen aus der Kinderheilkunde un ihren Grenzgebieten. 116ft 40, 1936, Berlin, S. Karger.

Lectures given in Spanish (August 12-17, 1935) at the International University at Santander, Spain, in the amphitheater of the Casa de Salud de Valdecilla.

#### I. INTRODUCTION

THE advances which have been made during the past thirty years in the cticlogy and experimental investigation of acquired applies in the etiology and experimental investigation of acquired syphilis have become very important in the presentation of the theory of congenital syphilis. In spite of these advances, widespread fallacies exist which have not yet been clarified. As in the field of tuberculosis, famous clinicians and pathologists, such as P. Ricord, R. Virchow, A. Fournier, A. Neisser, endeavored to determine the limits and nature of syphilis before the discovery of its etiologic agent and before satisfactory experimental animals were available. In spite of clinical experience, they reached false conclusions which have persisted and which even today influence some physicians. In both of these chronic and polymorphous diseases, whose differentiation from diseases clinically resembling them was once so difficult, a well-grounded study could begin only after discovery of their etiologic agents. By the introduction of exact methods of investigation Robert Koch, who died twenty-five years ago, first lightened the gloom of tuberculosis with the flame of his genius more than fifty years ago (1882), while only thirty years have passed since the discovery of the spirochete of syphilis (Schaudinn and Hoffmann<sup>1</sup>). By the introduction of experimental syphilis (Metschnikoff-Roux2), the serologic reaction (A.v. Wassermann3), and spinal fluid diagnosis,4 valuable supplements were found which, together with the discovery of Fritz Schaudinn, placed us for the first time on a definite basis regarding the recognition of the pathogenesis of congenital syphilis. In connection with proof of the curative and preventive action of atoxyl (P. Uhlenhuth, E. Hoffmann, Salmon, and others), Paul Ehrlich created modern chemical therapy, which, following the introduction of arsenobenzol (1910), has laid the foundation for the prevention of and for an efficient battle against congenital syphilis.

If I review, in four lectures, the greatest advances in a field which is covered by a voluminous literature, it seems to me better to consider more fully the new discoveries of worth rather than the older pathology and symptomatology. These new discoveries have altered our position in regard to this problem and have made us more optimistic, in spite of some erroneous views which have persisted. The time has come to draw

First discovery March 3, following joint research at the Berliner Hautklinik (Charlté), first publication April 25, 1905, in the publication of the Kaiserlichen Gesundheitsamt (see Wien klin. Wehnschr. 1935, No. 32 and Vortrage und Urkunden etc., Verlag S. Karger, 1930). Here there is an exact description of the discovery of the etiologic agent of syphilis (Appendix 122-124) as well as a reprint of the first four original articles.

In apes in 1901, in rabbits. Bertarelli and Volpino in the eye in 1906. Parodi in the testicle in 1907, and L. Hoffmann, Löhe and Mulzer in the skin of the testicle in 1908 first found the virus (primary syphiloma).

In 1906, on the basis of the complement fixation reaction of Bordet, in conjunction with A. Nelsser and C. Bruck.

<sup>\*</sup>After Quincke's discovery of the lumbar puncture, Rayaut. Steard, and others introduced its use, and Wassermann and Plaut supplemented it by the specific reaction. \*Salvarsan in rabbits in 1909 (in collaboration with Bertheim and Hata); in man in 1910; neosalvarsan in 1912.

conclusions, clearly and emphatically, from these advances and to make our goal the elimination of this once dreaded scourge, laying stress on familial and social problems. Many details are to be found in the new Handbuch, in articles by Rietschel, E. Müller, Péhu, Kerl, and others, while as yet the fourth volume of the French work "Traité de la Syphilis" (Jeanselme) has not been published. As the literature is voluminous and many publications are of doubtful value, I believe it better to limit myself to the accepted facts and views which are of practical import for the elimination of congenital syphilis.

Owing to the frequency of transmission of syphilis to the fetus, syphilis has always assumed a special position among the chronic infectious diseases. Premature interruption of pregnancy and expulsion of a macerated fetus are consequences of this disease which have been ascribed to a very early infection, explained by "germinative transmission" and even blastophthoria. This assumption was made by Paracelsus, who wrote in 1529, "Fit morbus hereditarius, et transit a patre ad filium." In a noteworthy manner, Ambroise Paré in 1633 said, "Souvent on voit sortir les petits enfants hors le ventre de leurs mères ayant cette maladie, et tôt après, avoir plusieurs pustules sur leurs corps; lesquels estant ainsi infestés, haillent la vérole à autant de nourrices qui les allaitent."

Such strictly clinical observations explain the choice of the term "hereditary," which was formerly so generally accepted that its exclusion from the terminology of many countries appears to be difficult. Nevertheless, this term should be avoided, because the transmission of the spirochete of syphilis has nothing to do with heredity, the laws of which are now known. Instead, the present term "congenital syphilis" has become fairly generally accepted. Objection has at times been raised to this designation because it suggests infection through conception, and the terms "syphilis innata" and "connatalis" have been suggested to replace "congenital syphilis." I support this change in terminology and E. Müller, Péhu and Kerl have cited the latter names in their new Handbuch articles. Thus I may designate as "syphilis innata" the severe fetal forms now called congenital syphilis in the French literature, and as "syphilis connatalis and postnatalis" the milder forms which first appear after birth. From these diaplacental infections, those infections occurring during and after birth must be distinguished as acquired infant syphilis, "syphilis acquisita infantum," and, as we shall see later, the rarer mixed infection, "syphilis binaria."

<sup>&#</sup>x27;in Arzt-Zieler, Haut- und Geschlechtskrankheiten, Urban und Schwarzenberg, 4,541 (bibliography here given).

Now being completed by Sézary (Marson et Cie., Paris, publishers).

'Quoted from C. F. Marshall, Syphilology, etc. (London, 1906, p. 217). As Rietschal stated, Fallopia, the personal physician of Popes Alexander I and Julius II, had already recognized the syphilitic fetus and infection of wet nurses (Jadassohn's liandbuch, 19, 1).

### II. PATHOGENESIS (METHOD OF TRANSMISSION)

Whether a germinative transmission is possible or whether in syphilis, as in all other infectious diseases, infection becomes established later in the course of pregnancy through the placenta and umbilical cord, is a question of decisive importance in regard to further problems, especially that of prevention. As will be seen below, the course of infection is explained in the latter sense by our investigations. The opposing views of certain physicians, who cannot renounce old familiar and beloved theories, similar to the opposition of Rudolf Virchow to Robert Koch's discovery, cannot seriously oppose the newly won facts.

A. Theory of Germinative (Paternal) Syphilis.—The studies of the late Rudolf Matzenauer in 1903, shortly before the discovery of the spirochete, had shaken the theory of paternal syphilis so strongly that many experienced clinicians were already turning from it. Although my teacher, Edmund Lesser, as well as E. Finger and others, strongly supported this theory of paternal transmission, which was contrary to sound reasoning and which confused rather than helped the young physician, I had known it to be incorrect even before Matzenauer's famous publication in Vienna. However, at that time, I refrained from opposing this theory out of consideration for my teacher. Since the discovery of the spirochete, this theory has become entirely untenable.

Because syphilis is usually introduced into the family by the father, the older physicians suspected that a "purely paternal transmission" could occur, thus sparing the mother from the disease, and that the "guilt" of the procreator would be visited on the children (and children's children). This supposition, which was indeed incompatible with the known contagious nature of the virus of syphilis, became strengthened in the minds of clinicians. Before the discovery of the Wassermann reaction, mothers of syphilitic children were at times found to exhibit no symptoms or clinical manifestations of syphilis, even after most thorough examinations. It was already known at that time that the tendency of syphilis was prolonged latency in the early as well as in the late stages. But the entirely asymptomatic course, the "silent infection," was only admitted later after animal experimentation (rabbits) by Kolle and others. Certainly Matzenauer had already referred to it and to the fact that in a series of mothers of definitely syphilitic children, suggestive and even positive signs (adenopathy, leucoderma, essential alopecia, etc.) could be demonstrated by a very thorough clinical examination. This idea of an asymptomatic syphilis later became confirmed by numerous serologic examinations and has given rise to the idea that every mother of a syphilitic child has either a latent or active infection,

E. Hoffmann, Actiologic der Syphilis, Springer, 1906, p. 42. The importance of spirochetes in the mother and fetus as well as in the fetal membranes is emphasized here.

and that she is the carrier of the infection. Statistics which support this are so frequently published and cited in texts that I need not discuss them here.

In support of the theory of paternal syphilis, which formerly Kassowitz, A. Fournier, etc., and even today Finger, Hochsinger, <sup>10</sup> Fischl, Almkvist, Mutzer, and others would not renounce, are a few observations which are regarded by critical clinicians only as rare accidents. Thus, families are described in which a syphilitic husband has been the father of a syphilitic child by a supposedly healthy wife, while she has later given birth to a normal child by a healthy husband, and all serologic examinations of the mother and child (spinal fluid, roentgen ray evidence?) have remained consistently negative. One such observation was published in 1929 by J. Almkvist, the well-known Swedish syphilographer. This was translated into French by Péhu.

Nov. 4, 1914, a mother gave birth to an infant weighing 2,950 gm. who had a syphilitic papular eruption and positive Wassermann reaction. Examination of the mother did not reveal any reason for supposing the existence of syphilis, either clinically or serologically. This woman has been serologically examined 36 times in the past 14 years, always with negative results. June 29, 1935, about 10½ years after the birth of the syphilitic child, she married another husband and was delivered of a child weighing 3,920 gm., completely healthy and showing no symptoms of syphilis. This infant and his mother have been followed by Almkvist; neither has presented clinically or serologically any evidence of syphilis. Thus this physician concludes that the syphilis of the first infant was of paternal origin.

The above case shows more than ten years' interval between the births of the syphilitic and the healthy infant. During such a long period the transmissibility of syphilis usually disappears spontaneously, thus making possible the formulation of the "laws of marriage" of the older clinicians. The birth of a healthy infant is easily explained by the long lapse of time and the fact that the mother probably had a previous latent or manifest syphilis, perhaps healing later spontaneously. Negative serologic reactions do at times occur in syphilis of long duration. Significant conclusion can obviously not be made on the basis of one or two rare cases.

This is still more true in cases in which treatment of the father alone has led to the birth of a normal child after or between the birth of other syphilitic children. Today, such observations must be regarded as coincidences, because formerly treatment consisted only of mercurials, which could influence the transmission of syphilis but slightly, as compared with salvarsan.

Through similar clinical observations, the opinion became established that the sperm of syphilitic men commonly contained and transmitted the germ of the disease. However, since the size of the spirochete in comparison with the sperm head has become known, this theory has had

rein Abhandlungen aus der Kinderheijkunde und ihren Grenzgebieten, No. 15, the old dectrine is presented by one well versed in this theory.

to be abandoned. The partisans of paternal transmission now consider a "granular virus form" to account for the infection of the ovum. That is also not justifiable, in spite of the intercession of Levaditi, Hochsinger, Meirowsky, and others.<sup>11</sup>

Further, through experiments on apes and rabbits, the "infectiousness of the sperm" of syphilitic men has been proved, and it cannot be denied that, in contrast to reported negative results (A. Neisser, E. Hoffmann and others), at times positive results ensue (Finger and Landsteiner, Uhlenhuth and Mülzer and others). These experiments cannot be of great value because, if the sperm flow contains many spirochetes, the mother will be infected by such a contagious disease before the ovum, which in early development is protected so well by Nature by virtue of its membranes and living metabolic processes.

All clinical observations support the fact that syphilis is usually transmitted by spirochetes occurring in erosions, etc., of the skin or mucous membranes, while it has not been proved that the sperm alone is infectious in men free from such lesions. During the secondary stage, men infect their wives by means of spirochetes transmitted from erosions, papules, and mucous membranes. Spirochetes frequently occur in the urethra, and I believe them responsible for the occasional infectious nature of the sperm flow.12 Nothing is definitely known about the spirochete content of spermatic fluid in late syphilis. However, I know of one significant fact bearing on this matter. Physicians who have acquired syphilis in the course of their professional duties (usually primary lesions of the fingers) and, in spite of a roseola, have remained free of genital lesions, do not often infect their wives, even when continuing marital relations during the course of the secondary period, when their infection was still undiagnosed. This observation, which I have occasionally made in physicians and also in nurses and laymen, is evidence against the virus content of the spermatic fluid, even during late primary and early secondary stages; this fact is important because of many repeated negative findings. So far as I know, infection of rabbits by repeated injections of naturally obtained spermatic fluid of an infeeted buck has not been successful.

Finally, the so-called exceptions of Colle's law formerly played an important rôle. They occurred very rarely, and not once were they described by reputable clinicians of wide experience. The appearance of an apparent primary (pseudoprimary lesion) on the nipple of the mother of a syphilitic child was considered a new infection, while today

<sup>&</sup>quot;On the basis of implantation experiments using the method described by Schaudinn, v. Prowazek, and E. Hoffmann, the rolled-up forms (formes en boucle et en pelote) were recently described by Levaditi, Schoen, and Vaisman as a stage of development of the Spirocheta pallida (Zentrulbi, f. Haut- u. Geschlechtskr: 52, 249).

<sup>&</sup>quot;Czerny and other pedlatricians emphasize the fact that in foundling asylums (e.g., Prague) the contagiousness of congenital syphilis is not great and transmission is rare. As the virulence of protozoa is enhanced by characteristic passage of insects, a similar augmentation of the virulence of Spirocheta pallida may be possible in weeping papules, eresions, etc. (under anaerobic conditions) which would be of importance in contact infection and may explain the greater frequency of genital lesions compared with extragenital infections.

we know that only a reinduration (superinfection) can occur on a latent syphilitic.12 Such exceptions to Colle's law are no longer heard. greater knowledge of symptom-free reinfection and superinfection, obtained from experimental syphilis, has aided much in the explanation of this fact.

The theory of paternal transmission had progressed far, as shown by the theory of "choc en retour." formulated by the great Ricord. Péhu interpreted this as an indirect infection of the mother by the sperminfected child, as well as infection by the father, and regarded this theory with scepticism. To us, this theory must appear exaggerated and erroneous; today it is considered only a curiosity.

Here may also be mentioned the theory of syphilis by conception (syphilis conceptionelle précoce), which assumes an especially malignant form of the disease when conception and infection occur simultaneously. Even in a definite postconceptional infection of a mother who was previously healthy at the time of conception, adherents of the theory of paternal transmission have regarded the infection as being carried from the sperm to the ovum, with subsequent infection of the mother through "choe en retour."

As well-known clinicians still cling to these erroneous views, the facts which contradict "paternal transmission of congenital syphilis" will be clearly presented once again. First of all, the records of very rare, doubtful cases are no longer tenable in the face of modern knowledge, even though occasionally they appear significant. We know today that syphilis is so contagious that were a syphilitic man to transmit spirochetes by his sperm to a woman, he would first infect her and not the Spirochetal infection of the ovum and not the more accessible mother is therefore to be regarded as improbable, if not impos-Also it is hardly conceivable that a holoblastic ovum. 14 such as the human, would continue to develop if it were syphilized, because even later, in the fetus, immunity is lacking or is so slight that with early diaplacental infection spirochetes overwhelm it and can cause its death. A matter of decisive importance is the fact that spirochetes have never heen found in the fetus of syphilitic mothers nor in the fetal portion of the membrances before the fifth month of pregnancy. Rare exceptions toward the end of the fourth month, such as the fetus described by Gräfenberg and others, are not definite, while others carefully described by Oluf Thomson, Paul Schneider, etc., showed nothing. If a germinative infection occurred, spirochetes would be expected to develop in such numbers in the fetus during the first half of pregnancy, that they could be demonstrated without difficulty in the first months of pregnancy.

<sup>&</sup>lt;sup>12</sup>D. Hoffmann, Dermat. Ztschr. 12: 491, 1905.

<sup>&</sup>quot;As interesting as they may be, the observations made by Levaditi on mereoblastic ova (spirochete of chickens) have no importance for human pathology; similarly, the experiments with pebrine (a disease of silkworms) have no bearing on the

How enormously spirochetes can multiply in very young animals, e.g., chickens, is shown by the inoculation of *Spirocheta gallinarum* into newly hatched chicks; the research done in my laboratory by Kroó<sup>15</sup> is also significant in regard to this question. The germinative—that is, the oogenic as well as the spermatogenic—transmission of syphilis may therefore be regarded today as entirely unproved. Attempts to preserve this doctrine by older and even by more recent clinical observations are of minor importance when opposed by the great mass of available research.

B. Diaplacental Infection.—As has been emphasized by G. Herxheimer in his excellent article (Wiesbaden, 1928) and in my papers (Hamburg, 1928, and Koenigsberg, 1929), only the diaplacental route of infection remains, and Matzenauer's statement, "Without a syphilitic mother there can be no syphilitic child," may today be considered entirely valid. Matzenauer's theory, which Rietschel and I have long supported (Handb. d. Hautkr. 19), that transmission first occurs by way of the placenta and umbilical cord during the second half of pregnancy, most frequently in the sixth and seventh months, can be amplified on the basis of new research, confirmed by Klaften in conjunction with O. Thomson, P. Schneider, and others. Thus, the earlier view that syphilis was the result of a germinative infection has lost favor, this chronic infection following the rule of transmission of the etiologic agents from the mother to the child.

The transmission of Spirocheta pallida occurs regularly from the infeeted mother to the fetus; in general, it occurs more intensively and more frequently if the mother's infection is fresh and severe. In cases of severe, untreated infection, this results in the early expulsion of a diseased and dead fetus. In the course of time, the intensity of the syphilis gradually diminishes, even without specific treatment, and children are born at term, manifestly infected or apparently uninfected. the latter sooner or later showing signs of syphilis. The birth of a completely healthy infant can occur between stillbirths or infected children. The "spontaneous gradual diminution of the intensity of syphilitic transmission," according to Kasowitz' rule, which in general holds good. is thereby broken. The cause of this lapse lies, first, in the fluctuation of intensity of the mother's infection and the number of virulent organisms which enter the blood stream, and, further, in the extent of localized infection within the mother's placenta, conditioned by the organisms in the blood. This irregularity of fetal infection is well illustrated by the fact that twins are not necessarily equally severely infeeted; indeed, one may be healthy and the other syphilitic. One such occurrence was reported in uniovular twins and, I believe, can be explained by the localization of foci of infection in the placenta and umbilical cord.

<sup>&</sup>lt;sup>12</sup>The chicks do not react clinically to the immense multiplication of spirochetes. Hofmann, Actologie der Syphilis, Springer, 1906, 42.

It has recently become recognized that habitual abortion during the first months of pregnancy is not always due to syphilis but to the same causes as in nonsyphilitic women, while stillbirths and premature births occurring during the second half of pregnancy (fifth and sixth months on) are suggestive of syphilis. However, in spite of this, in actual practice, abortions should always be investigated for the presence of syphilis.

The participation of the obstetrician in the investigation of and battle against congenital syphilis has become very important. In addition to the course of the pregnancy, the pathologic-anatomic changes which are found in the placenta and umbilical cord are of great significance and can frequently be shown to be specific by the presence of spirochetes. The placentas of syphilitic fetuses and of syphilitic children are usually abnormally large and heavy in proportion to the body weight of the child. I have termed this proportion of placental to infant or fetal weight the placental quotient. At the end of gravidity, it is usually 1:6 for the normal, 1:5 for the syphilitic, and even 1:4 and more in premature births, thus at least arousing suspicion of syphilis.16 The placenta also shows pathologic changes which consist of proliferation of capillary endothelium and stroma cells, diminution of intervillous spaces, the so-called abscesses in the villae, and vascular changes which are manifested as an obliterating endovasculitis, which Kaufmann found in 16 per cent of cases. Anemic infarcts, which Virchow first thought to be gummas, and infiltrates containing giant cells occur especially in the maternal portion of the placenta. Frequently the umbilical cord likewise shows perivasculitis, mesovasculitis, and endovasculitis with small cell infiltration, which is more pronounced in the adventitia and media at both ends of the cord. The focal arrangement stands out in a characteristic manner in and around the umbilical vein, which is frequently involved.

All these changes, in themselves not characteristic of syphilis, demand consideration, and further studies, such as dark-field examination and silver stains of sections, should be carried out in establishing proof of the etiologic agent. Spirochetes are frequently present in the walls of the umbilical vessels and can be found at times in scrapings of the intima and media of the umbilical vein which is generally involved severely. In the placenta, spirochetes are often as numerous in the fetal as in the maternal portion, although they invade primarily from the latter portion; this may be due to the influence of immunity developed in the maternal organism, as well as to its high oxygen content.17 The transmission of the anaerobic spirochetes into the fetal portion does not occur before the fifth month of gestation. Probably an occasional spirochete suffices to infect the fetus owing to an almost complete absence of immunity in

<sup>&</sup>quot;IL Hoffmann Dermat. Zischr. 54, 369 and 57, 145.

FIG. Hollmann therman, descar, 53, 500 and 51, 125.

The small number of Spirocheta pallida in the oxygen-rich placenta and in the blood, as well as their situation in the tissue, led me in 1905 to infer that the spirochete was anacrobic, a fact which Schaudin, at first doubted.

the latter, the severity of the infection being proportional to the invading masses of microbes (involvement of the vessel walls). This invasion can enter directly into the blood stream or, in addition, can occur through the lymphatic passages,18 in which case, as I stated in 1928, a sort of primary complex can develop in the fetal placenta and in the umbilical cord up to the liver vessels. Thus, occasionally, a specific phlebitis can appear in the infected liver (Beitske). By animal experimentation (rabbits), healthy placentas have been penetrated by the Spirocheta pallida and similar spirochetes (Philipp and others); this is not true for the larger parasites, such as trypanosomes. These tedious experiments, however, do not have any great significance when applied to human pathology. My hope that animals with longer periods of gestation (e.g., llamas) could be used in these experiments has thus far remained unfulfilled.

Transmission of Spirocheta pallida can occur until the end of pregnancy. The number of transmitted germs may depend on the age and intensity of the maternal infection and on the number of spirochetes still motile and present in the blood stream, as well as on the extent of localized infection in the maternal placenta. Thus, the protecting barriers to the fetal portion of the placenta may break down in the case of a maternal infection acquired shortly before or during pregnancy, with an ensuing high spirochetal content of the maternal blood resulting in numerous placental foci. The earlier this fetal invasion occurs (fifth to sixth months) with consequent greater invasion of the fetal blood, lymphatic and tissue routes, the more intense will be the infection of the fetus which is not yet protected by any immunity. Because of the absence of immune processes, an unchecked increase of parasites may occur in the fetus and thereby cause its death. Involvement of vessels with narrowing of their lumen, as observed in the syphilitic placenta, results in deficient nourishment. Transmission of spirochetes may occur long after the original maternal infection, due to the fact that acquired syphilis may run a course of exacerbations and, when untreated, recurrences are possible during many years.

On the other hand, even with a fresh syphilis of the mother which has not been specifically treated, transmission may occur late or, more rarely, Thus may apparently normal or really normal children be born. The fact that the former frequently show evidences of syphilis four to eight weeks or within the first four years after birth has given rise to the opinion that transmission of spirochetes first occurs shortly before birth or-what may be rare-during it, due to loosening of the placenta (II. Rietschel).19 This type of congenital syphilis, becoming

BH. Rietschel first suggested this possibility in 1913.

<sup>&</sup>quot;Late transmissions are frequently reported, as for example, I. Levin considered an infection as occurring fourteen days before birth on the basis of the appearance of a primary lesion on the mother ten days later (ten days postcoitus and four days prepartum') and the infant having Coryan syphilitica twenty-five days after birth, and an exanthema and weakly resitive scrologic reaction forty-four days after birth. (Zentralbi, f. Haut- u. Geschlechtskr 51, 589).

recognizable some weeks or months after birth, could be designated as syphilis postnatalis, or as syphilis congenita, innata, and connatalis.

All degrees of severity of infection are evident, ranging from a macerated fetus and severe visceral and bone syphilis of affected children (syphilis innata) to the apparently healthy infant (syphilis connatalis or postnatalis asymptomatica). These types are explained by the manner and severity and, above all, by the time of invasion and numbers of spirochetes invading through the maternal placenta whose protective function eventually fails to a greater or lesser degree. It is not clear as to the extent to which antigenic substances traversing the placenta play a part in mitigating the infant infection.

It should be further emphasized here that the severity as well as the frequency of fetal syphilis has significantly become reduced during the last decades. This fact is cited in the new Handbuch and in many individual articles and is ascribed to salvarsan therapy during pregnancy, a therapy which has also aided in a reduction of syphilis in general. Before I discuss this further, some questions of acquired infant syphilis must be considered.

C. Binary and Acquired Syphilis.—Pasini questioned whether there was a sharp distinction between congenital and acquired syphilis of the newborn, and I explained the possibility of mixed infections, i.e., a binary congenital syphilis.

All infections occurring by hematogenous or lymphogenous routes and not exogenous (with or without a primary lesion) are considered as syphilis congenita; infection takes place through the umbilical cord, which may present a phlebitis. Rare cases of deep or superficial, chancrelike, umbilical ulcers, which, according to Hutinel, L. F. Meyer and others, appear about three weeks after birth, have been regarded as lymphatic infections occurring through the umbilical cord. Similar forms of infection, rarely noted, approach acquired infant syphilis in appearance and are difficult to differentiate from an exogenous infection of the umbilicus occurring during or shortly after birth.

As I have pointed out in previous articles, a double infection is possible, giving rise to syphilis congenita binaria, only one case of which, reported by Schilling and V. Hoffmann, one case of which, reported by Schilling and V. Hoffmann, as I able to accept as definite. This mixed form can occur when a child, infected before birth by diaplacental transmission of spirochetes from the mother, receives a second or superinfection of spirochetes through the skin during the passage through a birth canal containing infectious papules or erosions. This superinfection can be manifested by a primary on the head, or more rarely elsewhere, but may occur asymptomatically. The spirochetes, derived from the same source, namely, the still infectious mother, reach the child by two different routes: most important, before birth through the umbilical cord, and then later through the skin at time of delivery.

<sup>&</sup>quot;Jadassohn's Handb, d. Haut- u. Geschlechtskr. 17/3, 168.

Naturally there remains the possibility that an exogenous infection after birth can originate from the same or from another source of infection (wet nurses, nurses, etc.).

Such infections "en passage" are very rare, A. Fournier stating that he had never seen one. In my article on binary syphilis of nursing infants,21 I referred to ten cases of proved primaries on the heads of nursing infants and believe that these are frequently overlooked because they are often insignificant and the regional lymphadenitis may be minimal. Consequently, the question whether there is a sharp borderline between acquired and congenital syphilis in infants deserves more consideration, and our best efforts must be given to the study of the possibility of superinfection and to careful investigation of binary syphilis of the newborn. Thus might be explained the appearance of keratitis profunda, etc., following what would appear to be an acquired syphilis in infancy.

Tarnowsky described binary syphilis of older individuals with signs of late congenital syphilis, which should be differentiated from binary syphilis of nursing infants and should be considered as a reinfection or superinfection of an older congenital syphilitie, in whom the skin immunity, with or without specific therapy, has decreased to such an extent as to permit a true primary or a pseudoprimary lesion. The possibility of a symptom-free superinfection should always be considered; also, reinfection without an obvious primary lesion may prove to be more important than was formerly thought in doubtful cases, causing late recurrences after an apparently successful cure of adults and of children.

Most pediatricians regard acquired infant syphilis as rare and proportionately unimportant; as Czerny emphasizes, it usually runs a less severe course than in adults.22 Unfortunately erroneous views prevail which have been represented by illustrations and descriptions in wellknown textbooks and thereby have been uncritically disseminated. Pictures of older children of six years or more with alopecia microareolaris. which is a typical early manifestation of an acquired syphilis and is encountered in adults only in the first year, are presented as "late recurrences of congenital syphilis" (Ledermann in Jadassohn's Handbuch.23 E. Müller in Pfaundler's Handbuch, Feer.21 etc.). Also, leucoderma and vegetating condylomas occurring in well-nourished infants and older children are indicative of an acquired (or binary) and not a congenital infection.25 The primary lesion may frequently be concealed. for example, on the tonsil, and is easily overlooked.

Deutsche med. Wehnschr. 1929, 1289; Schweiz, med. Wehnschr. 1929, 1213; and Dermat Ztschr. 54 (1928), 369 and 57 (1930), 150.

=Other authors, such as Rietschel, do not share this view.

=Jadasschn's Handbuch, 19, 73.

<sup>\*</sup>Lehrb., 9, Edition 1926, 723 (Condyloma).

Experienced pediatricians, such as H. Rietschel, believe that such condylomata are never observed as an original lesion, but rather as a recurrent lesion after the first year of life, and then only rarely.

D. Frequency of Congenital Syphilis .- The occurrence of congenital syphilis has been significantly reduced. E. Müller, Klaften, Péhu, Lomholt, and others have made statistical studies and have attributed this reduction to successful treatment with salvarsan preparations, which has also caused a decrease in the formerly marked polymorphism and severity of congenital syphilis. The statistics presented by authors in different countries vary considerably.

In many countries (e.g., Biazil, Russia, etc.) they are higher than in Germany Years ago Buschke estimated the number of stillbirths in Germany as 20 per 25,000, and Barsch as 20 per 10,000 According to the German census of 1927, there were about 7,500 living children with congenital syphilis In the children's chinics, from 2 to 4 per cent of infants were found to be syphilitic. In England and France these figures are higher and reach 10 per cent, and in France and its colonies even 20 per cent and more To be sure, doubtful cases (hereditary distrophies, etc.) have been included. The number of premature and stillbirths due to syphilis was given as 50 to 90 per cent by Weber and Reischig, Reischig tound S11 per cent and Grafenberg found 92 per cent of the stillborn to be macerated The mortality of the infants born alive was high, Noeggerath showed that it was from 50 to 67 per cent in hospitals, from 24 to 35 per cent in nursing homes, and from 15 to 19 per cent in out patients (those less severely involved). The greatest number of these infants died in the first year, especially during the first four months. The devastating effect which syphilis exercises on progeny is shown by Hochsinger's great work, he followed 266 pregnancies in 67 families and found that 466 per cent of the pregnancies resulted in premature stillbirths, 28 6 per cent in infant mortality within the first year, while only 248 per cent of the infants remained alive Gammeltoft found only 7 (35 per cent) healthy children among 201 children of untreated syphilitie mothers. Hata could prove only 5 healthy children over five years of age in 100 syphilitic marriages

These few but startling figures suffice to show the devastating effect of syphilis on progeny before the introduction of modern therapeutic meth-

Another arresting fact is the percentage of pregnant women who have syphilis This was investigated by Blumenthal and myself in 190826 and also by others since then.

The figures obtained ranged from 8 to 10 per cent, and in Halle, reached even up to 20 per cent, they fell to 5 to 6 per cent and are now still lower (4 per cent) On the basis of compilation, Klaften estimated the average frequency of syphilis among pregnant women in Europe as about 45 per cent to 55 per cent; in America, 6.5 per cent. These figures have been greatly reduced wherever there is satisfactory In 1926 27 Philipp and Richter2° found 65 syphilitic children among 5,028 births in the Berliner Franchlimk, which is scarcely 13 per cent. In 1931 32, there were only 22 syphilitic children among 4,073 births, or only 0.5 per cent. The number of macerited syphilitic stillborn decreased during this period from 42 in 1926 27 to 7 in 1931 32, which fact is still more striking.

In Denmark, where the statistics are exceptionally accurate, due to an excellent central card index system, the yearly census of congenital syph-

<sup>\*</sup>Dermat Ztschr. 15, 23 and 17, 1 and 82

München med Wehnschr. 1933, 1540.

ilis has dropped from 280 in 1920 to 29 in 1931 (Lomholt<sup>28</sup>). I understand that in Vienna, in spite of weak doses of salvarsan (only 0.3 gm. of neosalvarsan per week) used in the treatment of pregnant syphilitie women, there is a disappearance of the macerated fetus, as well as a significant reduction of congenital syphilis, a fact noted by different authors. The statistics of the northern countries are similar to the Danish, thus demonstrating the success of treatment.

There is much in the literature about the transmission of syphilis to the second generation (termed by many, the third generation).

That an insufficiently treated or an untreated woman with congenital syphilis can exceptionally transmit syphilis to her child is admitted by clinicians, and a compilation made by Feige under my direction and newer studies show that a few cases may meet the rigid requirements of Fournier. Finger, and others. That transmission is also possible to the third generation (also termed the fourth) is asserted but has not been ascertained. These questions cannot be further discussed here because they have no bearing on the problem which interests us and, due to our modern therapeutic knowledge, are no longer as important as formerly.<sup>29</sup>

E. Doubtful Infections (Malformations, Hereditary Dystrophies, and Suphilis Larvée).—Finally there is another question, much discussed in the French literature, as to whether syphilis can engender monstrosities, malformations and dystrophies. This question has been exhaustively treated and criticized by Péhu. There is also the question as to whether a syphilitic toxin is capable of impairing the germ plasm, thus producing a blastophthoria. In my articles (1928-29), I opposed the idea that injury to the germ plasm can result without a diaplacental transmission of Spirocheta pallida. It also appears to me that this stand. already supported by Husler and others, is justified and I believe that it is worthy of being reemphasized. Whoever considers such a vague theory<sup>30</sup> must admit that syphilis by its influence on the germ plasm would have greatly damaged the human race during the last hundred years in the countries in which it is widespread. We know, however, that children of otherwise healthy syphilitic parents who are no longer infectious can be entirely normal. Indeed it is remarkable that extremely good-looking and healthy children have been born into otherwise unblemished families of old syphilities and paralyties, when marriage occurred after loss of transmissibility of the syphilis. The regularity with which healthy children are born, after intensive prenatal therapy with modern preparations (neosalvarsan, bismuth), supports this view.

The statements about the occurrence of monstrosities, malformations, and dystrophies are likewise derived from the experience and imagination of older clinicians and are vague and far-reaching and in need of

Dermat. Wchnschr. 100, 173.

Schönfeld: Dermat, Ztschr. 72: 119.

<sup>\*</sup>Fr. v. Miller formerly supported this theory on the basis of several observations in syphilitic families, which, however, can be explained otherwise.

revision. When syphilis was still more rife, and in regions where it was widespread (Paris, Morocco, etc.), even great clinicians ascribed unrelated conditions to syphilis. Thus Lewin once believed that maculae caeruleae, which are due to pediculosis, were a special type of syphilitic exanthemas, while in France, vitiligo, alopecia areata, the tubercle of Carabelli, and many other conditions were ascribed to syphilis. famous A. Fournier, who first included tabes, general paralysis and aneurysms as syphilitic manifestations, also ascribed numerous dystrophies of the teeth and other organs to syphilis, thus making, in addition to his observations of lasting value, unfortunate statements which have proved to be completely fallacious. It is still held that tuberculosis, rachitis, and other ills can occur on the basis of a congenital syphilis; a lamentable interpretation which, similar to the error of the great Hunter, has resulted in serious consequences. Recently French authors, such as Hutinel and others, considered such disturbances as residues of persisting infections of the infant and due to a specific involvement of the endocrine glands. Schneider, in his article in 1928, collected and reviewed the pathologic changes and spirochetal findings in these glands; also E. Müller, Péhu, and Kerl mentioned them. Interesting as this problem may be, I cannot discuss it further because of my limited personal experience. J. Darier in his excellent text (1928) included, in addition to "hérédosyphilis virulente," the "hérédodistrophies"; he characterized them as "troubles of physical development, a disposition to malformations such as an alcoholic or tuberculous father might cause," and said that these hereditary dystrophies can occur with or without a congenital syphilitic infection.

It is a recognized fact that certain severe dystrophic manifestations, such as the cicatrices of Parrot and other stigmas of the teeth, bones. sensory organs, etc., are evidence of congenital syphilis. These are explained by a lower degree of spirochetogenic involvement. If monstrosities, malformations, and dystrophies in syphilitic families occur without diaplacental transmission of spirochetes, they cannot be ascribed to syphilis. In this respect, it seems to me that the viewpoint accepted in Germany (Rietschel, E. Hoffmann, and others) is critical and correct. Whoever maintains a relation between syphilis and dystrophies must demonstrate the cause and prove the presence of the etiologic agent itself or its acknowledged consequences (inoculation, spinal fluid, serologic reactions, etc.). Because syphilis is extremely polymorphic in its manifestations and because of the possibility of simulation of other diseases (it has been termed the "great imitator"), the opinions of the French school should not be shared when it comes to diagnosis and delimitation. Instead, the rule, "Consider syphilis," should always be followed. such vague and insufficiently proved theories, which still persist in France, of the "dystrophic sequences of syphilitic toxins" and the influence of hereditary factors were seriously admitted, the progress made

by the research of the last three decades would be lost. The theory of "syphilis larvée" and Péhu's fourteen subdivisions, which include all the dystrophies and malformations as well as monstrosities in the various organs, would permit the possibility of a syphilitic origin for all human pathology, as Péhu himself admitted.

Rietschel devoted an article (Med. Klinik, 1931) to a critical résumé of these questionable doctrines and cited reasons why such a position is uncritical and untenable from a clinical standpoint.

Today it is a requisite of medical science to establish more stringent diagnostic criteria for the hereditary dystrophies and to eradicate exaggerated and uncritical theories. Only where the Spirocheta pallida can be found, or definite manifestations of it can be proved, are dystrophic processes to be considered as specific. All other dystrophies and malformations should be investigated on the basis of familial inferiority (mental or otherwise) or of true toxic causes (alcohol?) and, even if they are present in the same patient along with congenital syphilis, they should not necessarily be ascribed to the syphilis.

Before a syphilitic toxic influence from the mother to the ovum or fetus can be established, experimental proof on pregnant animals (rabbits) must be obtained. This could be done by repeated injections,. before and after coitus, of macerated organs rich in spirochetes-after heating to the death point of the spirochetes. Similar experiments could be carried out with alcohol and other substances having a possible influence on heredity. The assertion made by prominent clinicians-I mention here only R. Sabouraud, the world famous mycologist-that the abnormal tubercle of Carabelli be regarded as a sign of congenital syphilis shows how misleading purely clinical observations and statistics In countries where syphilis was, or still is, widespread, it is often present along with other diseases, as well as tuberculosis, and may be so masked by them that false conclusions are understandable. difficulty of correcting such errors is repeatedly shown in the history of medicine, and not infrequently even the most outstanding clinicians and pathologists (A. Fournier, E. Finger, R. Virchow) have at times held on to opinions in the realm of the chronic infectious diseases (syphilis, tuberculosis), which were later proved erroneous. In the French literature the opinion is held that tuberculosis can be considered only when it can be proved to be the result of infection with Koch's bacillus. When the same requirements are accepted for the Spirocheta pallida, a lengthy and violent controversy will end abruptly.

<sup>&</sup>quot;According to Pchu. hérédosyphilis larvée can be manifested by : (1) developmental disturbances, (2) nutritional disturbances, (3) endocrine disturbances, (4) osteoarticular manifestations, (5) nervous involvement, (6) digestive syndromes, (7) hepatic syndromes, (8) respiratory syndromes, (9) cardiovascular affections, (10) renal syndromes, (11) cutaneous manifestations, (12) blood changes, (13) involvement of the lymphatic system, (14) congenital malformations.

## III. PATHOLOGIC ANATOMY

Only a few important points of general pathology will be presented here, the subject having been thoroughly discussed by G. Herxheimer and P. Schneider in their Wiesbaden publications.

A. General Considerations.—Shortly after their transmission to the fetus, during the fifth month of pregnancy or later, the spirochetes multiply in the fetal organism without producing a reaction and disseminate through the fetus in immense numbers. To a much less degree. this is also true for acquired syphilis, where a severe, occult proliferation is present, not only in the early incubation period before the appearance of the primary lesion, but also in the secondary period in the roseolas and papules, etc., which are hematogenous in origin. As I have emphasized for thirty years, tissue reactions, not only the inflammations that are recognizable microscopically, but also the clinical manifestations, occur considerably after the invasion of the spirochetes. We know today that an asymptomatic infection32 may persist which merits attention in connection with gravid and congenital syphilis. As I have explained, the limited numbers of Spirocheta pallida in the blood and in the maternal placenta are due to the high oxygen content which destroys the anaerobic spirochetes; but under anaerobic conditions in the macerated fetus, an unlimited multiplication of spirochetes can take place. The opinion that this unchecked proliferation occurs after death has only been partially ascertained; as soon as there is a lack of oxygen due to edema and constriction of the lumena of the placental vessels. favorable cultural conditions prevail in the fetus, and, owing to lack of immunity, an unlimited increase of the microbes takes place. Expulsion of the fetus occurs several weeks after its death, thus affording in its oxygen-free tissue a great opportunity for unlimited multiplication of spirochetes. This finally results in partial decomposition of the fetus as a consequence of maceration following fermentative processes. G. Herxheimer has justly emphasized the anergy present in the young fetus of this type; and transmission of protecting immunity from the mother through the diseased placenta cannot really be considered when such severe endovasculitis is present.

The histological pathology of congenital syphilis is similar to that of acquired and experimental animal syphilis. It is distinguished by an inflammation of the blood vessels which may involve the walls of the veins, arteries and lymph vessels, even the capillaries and lymph spaces. The Spirocheta pallida, as I have emphasized since 1905, is a lymphatic and connective tissue parasite which behaves differently than the blood spirochetes. In spite of my repeated references to this fact, this difference is underestimated, as is the importance of the anaerobic tendencies of the Spirocheta pallida.

<sup>&</sup>quot;Experimentally proved by Kolle and others in mice and rabbits,

It does not seem, therefore, justifiable to speak of a septicemia in congenital or even acquired syphilis (septicémie syphilitique primosecondaire23). Proof of the presence of Spirocheta pallida in the oxygenated blood stream is very difficult in the living child, even in the most severe forms of congenital syphilis.34 Anaerobic Spirocheta pallida do not thrive in the blood but escape from the blood stream as quickly as possible, and are much more frequently found in the endothelium and perithelium of the blood capillaries and lymph spaces, and in the vessel walls, often surrounding the vasa vasorum. The endothelium becomes irritated, with resultant edema, proliferation, and hypertrophy; this has been determined experimentally in my laboratory during the primary incubation period of syphilis in rabbits, by G. Armuzzi, a student of mine for many years, who carried out my suggestions carefully. In the perivascular lymph spaces and in blood and venous thrombi, which have a low oxygen content, occasional or numerous Spirocheta pallida can be found, and also a few in regional lymph glands as early as twentyfour hours after infection, while they have been found in the spleen forty-two hours after infection by silver staining of sections (my student, Emil Zurhelle).

The true cytotropic reaction, which appears in addition to the endovasculitis, mesovasculitis, and perivasculitis, follows as a more or less allergic reaction, is related to vascular endothelium, and is considered by Aschoff as a defense mechanism of the reticuloendothelial system. This reaction is not uniform but appears in isolated islands, so that free zones always remain between the foci of perivascular infiltration. This focal distribution is also characteristic of the nests of spirochetes and is reflected in the histologic picture. In addition, there appears a unmistakable sclerotic change of the collagenous tissue, which in rabbits is accompanied by a myxomatous exudation, and in man by lymphedema and a less noticeable degeneration of the connective tissue.

The characteristic cell picture of syphilis does not consist of a pure plasmoma, as Unna assumed. Cell counts of tissue from chancres and later syphilomas, which have been made by various French authors (Nanta, Laurentier, and others), show from 35 to 63 per cent small lymphocytes, about 10 per cent large lymphocytes, and 10 per cent each of mononuclears and plasma cells; however the number of plasma cells is usually considerably greater, according to my experience and that of other German pathologists and syphilologists. In congenital syphilis, plasma cells are at first absent and later are more rarely found than in acquired syphilis.

French authors further assume a proliferation and even a wandering of the endothelium. They emphasize that giant cells, which are more

<sup>&</sup>quot;Sézary; Traité de la Syphilis (Jeanselme) III, 65.

<sup>&</sup>lt;sup>21</sup>I sometimes found them in dark-field examination in severely involved nursing infants (Berl. klin. Wchnschr., 351, 1967).

frequent in the many lupoid forms of syphilis and even involve vessel walls, are of endothelial origin. I frequently have seen convincing examples of this in small vessels (veins) which are being destroyed by endovasculitis.

B. Bone Involvement .- In the dearth of other symptoms, the bony involvements have become very important in the detection of fetal and early forms of congenital syphilis, not only because of their spirochetal content, but because they are recognizable roentgenologically. The most important form is the classical Wegnerian involvement of the epiphyscal borders of the long bones (femur, tibia, etc.) which is also manifested in the cartilaginous borders of the ribs and elsewhere. These changes can occur from the fifth fetal month onward. The great frequency of bone involvement and its significance in Parrot's disease (a pseudoparalysis due to epiphyseal separation) give it a special value for syphilologists, pediatricians, obstetricians, and pathologists. Next in importance to osteochondritis is periostitis syphilitica; this form may begin in fetal life but usually appears somewhat later. In addition, German authors mention the ostcomyclitis fibrosa rareficans of Pick, and Péhu also cites a productive hyperplastic form. A type characterized by transverse shadow bands (Klaften) has recently been reported which can be recognized roentgenologically and which occurs following prenatal specific therapy in Wegner's disease.

On the basis of thorough researches by O. Thomsen, P. Schneider, L. Pick, M. Péhu, and others, it may be said that spirochetes are present in their classical form in the growth centers of the bones, but not before the fifth month of pregnancy. In the absence of any reaction the spirochete is the only certain indication of a progressive but otherwise latent infection; the stratum of cartilaginous development is its site of predilection, while this form of involvement does not occur in the membranous bones. Osteochondritis regularly occurs symmetrically, is often recognizable by roentgenographic examination before and at birth, and is easily differentiated from rachitis up to the third month. In the course of the first three or four months, the osteochondritis recedes spontaneously and disappears as a generalized symmetrical involvement, while other forms become more pronounced (periostitis, localized lesions, etc.).

Thus, ostcochrondritis syphilitica is not, as its name signifies, an inflammatory process from the beginning, but is a characteristic alteration at the border of the developmental zone between the diaphysis and epiphysis of the long bones, ribs, etc., the ossification of which is disturbed in the cartilaginous stratum. The normal epiphyseal borders, which ordinarily appear as a regular narrow white line, become an irregular, zigzagged, yellowish white streak seldom more than 4 mm. in width. At a further stage in development, a striking zone of yellowish tissue arises which projects in tonguelike forms of different lengths into the epiphysis. Under the influence of the Spirocheta pallida, which

causes little or no reaction in the fetal organism, bone formation is disturbed and greatly delayed, while the cartilaginous columns develop in the usual manner. Gratelike arrangements of calcified cartilage appear in the widened zones of calcification, the so-called "Kalkgitter" or calcified grate, between which normal cartilage remains. With severe degrees of involvement, in the course of time, a band of granulation tissue, which arises from the connective tissue of the young bone marrow, is interpolated between the bones and the zone of calcification. results in a spongy connection between the bony diaphysis and the cartilaginous epiphysis, and at times in a complete epiphyseal separation due to a fracture in the region of the "Kalkgitter" or at the border between the zone of calcification and uncalcified cartilage, thus producing the clinical picture of Parrot's pseudoparalysis. This anatomic process is usually more frequently and more marked in the lower extremities at the distal ends of the femur and tibia, while the hip and proximal ends of the tibia and humerus, as well as the radius and ulna, are less frequently and less severely involved. The ribs and smaller round bones are also more or less altered, as can be demonstrated roentgenologically (L. Pick and others). Parrot's pseudoparalysis shows a preference for the upper arm, which is easily traumatized. These sequences, which do not always occur in a regular order (Wimberger), demonstrate that primarily the lower extremities and wrists of the newborn merit roentgenographic study (Péhu and others35).

The degree of involvement recognizable anatomically as well as roent-genologically has been divided into three stages. In the first stage, the provisional zone of calcification is somewhat broadened. In the second stage, it is 3 or 4 cm. wide and is visibly serrated with granulation tissue projecting into the region of the "Kalkgitter" zone. In the third stage, in addition to the other disturbances named, this granulation tissue has so increased that it results in sponginess and even in epiphyseal separation (pseudoparalysis).

This gradual process, which is very marked in the premature and the newborn, is demonstrable to a less extent by roentgenograms of the fetus in utero. Péhu and Policard believe that at first a clear zone, broader than normal, and near the diaphysis is characteristic of the roentgenogram, and that longitudinal serrations in the "Kalkgitter" zone become visible as dark lines resembling pencil marks. This roentgen evidence is often still more striking because of the presence of double-contoured dark stripes.

Periostitis syphilitica can likewise begin in intrauterine life but occurs less commonly in the first months, becoming marked usually after the third month of life, and assuming more importance in later childhood. This condition is manifested in the long bones and clsewhere and is

<sup>\*</sup>Gool illustrations are found in L. Pick's article, "Angeborene Knochensyphilis," in the Handb, d. pathol. Anat. (9/1), and in other textbooks, and are therefore not included here.

recognizable roentgenographically, in consequence of its ossification, as a cup-shaped dark line. Periostitis ossificans also appears in the phalanges and skull bones during childhood. Also periostial hyperostoses can be present on the skull in early life; they later produce characteristic stigmas, especially of the tibia (saber shin).

Schneider has called attention to two types of osteochondritis which are not strictly delimited; namely, the passive type with marked spirochetal infiltration of the fetal tissue, and the later active type, in which more and more reactive processes slowly appear with formation of granulation tissue.

C. Active and Passive Process (Miliary Syphiloma).—Schneider's division into passive and active processes is basically important for the changes in other organs. Thus, many organs are infiltrated by immense masses of spirochetes without evidence at first of a perivascular or an interstitial inflammation, while later, if the defense mechanism in the last fetal months or at the time of birth develops slowly and thereafter becomes stronger, these reactive processes stand out more prominently. A dense spirochetal infiltration is found, for example, in the suprarenal gland, where the microbes are ordinarily found between the cells. Here, as French authors have pointed out, a marked opposition exists to the ultravirus, which lies within the parenchymal cells or within the nuclei. The difference between an early anergic reaction, then a hypoallergic reaction, and rarely an allergic reaction, is decreased about the time of birth and later becomes still less; then the so-called miliary syphilomas and nodular pseudogummas can occur in addition to an interstitial proliferative inflammation. These pseudogummas were formerly considered to be veritable gummas (R. Virchow and others), but can be differentiated from gummas by their extraordinarily rich spirochetal content. Indeed, the first case of congenital syphilis in which I found Spirocheta pallida in the liver, lymph glands, etc. (spring of 1905), was distinguished by such pseudogummas.36

Miliary syphilomas, which I have produced experimentally in rabbits,37 occur as small nodules most frequently in the liver, but also in other organs (bones, etc.) and consist of polymorphic, degenerated. occasionally necrotic cells, and usually contain spirochetal colonies which can be stained by silver methods. Similar in structure are the larger nodules, which resemble gummas more closely; whether a hyperallergic inflammation has played a part in these as in the true gummas appears doubtful in view of their rich spirochetal content. The so-called thymus abscesses of Dubois, as well as the characteristic pneumonia alba, contain large numbers of spirochetes.

Berl, klin, Wehnschr, 1905, 728 and 1022-5.

<sup>&</sup>quot;I found miliary nodules containing giant-cells in the tumorlike, older primaries in the rabbit cornea. (Dermat. Ztschr. 41, 236, Plate II, Fig. 3).

Unfortunately, it is not possible for me to enter further into these interesting pathological changes and their significance. I may, however, refer to articles by G. Herxheimer, P. Schneider3s and to the new Handbuch.

#### IV. CLINICAL MANIFESTATIONS

In connection with this general presentation of the pathogenesis and frequency of congenital syphilis, its symptomatology, which is easily found in textbooks, will only be mentioned briefly before I discuss the early diagnosis and treatment. As has already been stated, the severe symptoms, which previously were so frequently encountered by clinicians in their classical forms, have become rarer, and the picture of congenital syphilis has changed much more than that of acquired syphilis, in that it has become essentially more uniform and presents fewer symptoms.

Pathologic changes present in the dead fetus, placenta, and umbilical cord are of interest primarily to the obstetrician and pathologist. Because they have already been discussed, I will only mention that they result in the expulsion of the macerated fetus, or in the premature birth of syphilitic children, who are retarded in their development. A macerated fetus occurs rarely in the fifth, usually in the sixth to seventh, month of pregnancy: the living infants are delivered at this period. As already mentioned, with a young macerated fetus, there is a complete absence of reaction on the part of the tissue in spite of the immense numbers of spirochetes. Foci of spirochetes are present in the cartilaginous borders of the long bones, as well as changes indicative of the osteochondritis of Wegner. The resultant widening and irregularity of the cartilaginous border is diagnostically the most important sign of fetal syphilis. The chemistry of the developmental processes has been considered as an explanation for the fact that the spirochetes settle in these locations, after having previously flooded the liver from the blood stream. According to Schneider and others, the spirochetes occur here in large numbers and also at times, as Bertarelli found, in the osteoplastic centers.39 Similar residual or inactive foci-also in the periostium, etc.-are of significance in the explanation of persistent positive serologic reactions, or reactions becoming positive upon provocative treatment; if the foci are small and walled off, a continuing negative serologic reaction can occur, though this is rare.

A. Severe Forms of Involvement .- Osteochondritis is often accompanied by a severe nutritional disturbance, which is evidenced by the senile, atrophic appearance of the fetus and of the child. The color of the skin is a peculiar brownish yellow with gray undertones; in addition, there exists a striking pallor and emaciation. In very severe infections, there is a simultaneous involvement of the palms and soles by a pem-

This author presents numerous excellent illustrations.

<sup>&</sup>lt;sup>31</sup>E. Hoffmann: Atlas der ätiologischen und experimentellen Syphilisforschung, J. Springer, 1908. Plate 24, Fig. 2; here many other illustrations of congenital syphilis are found.

pargoid syphilide, which in typical cases consists of pea-sized vesicles, first clear, then cloudy, and rarely containing blood or pus—the "pemphigus syphiliticus" of the older syphilologists. The vesicles are surrounded by a ham-red to copper-colored zone of infiltration; in contrast to the pyogenic pemphigus of the newborn (impetigo neonatorum) which involves the trunk, the base of the syphilitic vesicles is compactly infiltrated and numerous spirochetes can be easily found in scrapings of the floor of the vesicles.

The coexistence of osteochondritis and pemphigoid syphilides, which at one time was much more frequent, is characteristic of the severe and early diaplacental infections. In such cases in which the pemphigoid eruption extends further and may even involve the entire cutaneous surface, at times a papulocrustaceous syphilide develops, and a visceral syphilis is also present in the liver, spleen, adrenals and in many other organs. The visceral involvements are usually more severe than the cutaneous manifestations; however there is an exception in the case of the pemphigoid syphilide which is a manifestation of syphilis congenita gravis. Between this severe form and the other specific exanthemas, there is a gradual transition, resulting in less severe visceral as well as external symptoms.

The cutaneous manifestations can be very polymorphic, as in acquired syphilis; but their regular sequence and typical morphology may be altered. In children with marked visceral syphilis whose severe fetal infection extends into the nursing age, as Huebner aptly stated, in addition to an irregular, coppery, atypical roseola and palmar and plantar papules, the diffuse, superficial, infiltrated syphilides are an especial indication of recent and severe infantile syphilis. These infiltrations, which may be as large as the palm of the hand, frequently occur on the face, especially around the mouth, and there result in rhagades of varying depth, which later leave characteristic cicatrices (Parrot) as stigmas. Also similar diffuse infiltrations are frequently noticed on the palms and soles and are characterized by their hamlike color. They are less common elsewhere (anus, buttocks). In addition to the coppery, irregular, and frequently atypical roseola, they characterize a severe to medium-severe infection. Macules, maculopapules, and crusting syphilides, which first appear in the less intense infections some weeks and months after birth (syphilis congenita postnatalis), will not be discussed further; they deviate from the appearance of acquired syphilis more or less by their atypical appearance and the absence of the more regular sequences of acquired syphilis. Even ulcerating ecthyma-like syphilides can occur early, and psoriasiform lesions and an infiltrated eruption similar to crythema multiforme (hyperallergy) are also occasionally described, as well as the appearance of infiltrated early gummas.

<sup>&</sup>quot;Stroscher, Dermat. Zischr. 1910, 17, Plate 3.

Another manifestation is the rare but symmetrical perinychia or paronychia on several or all the fingers, from which spirochetes can easily be demonstrated. These lesions, characterized by a brown to ham-red infiltration, can appear early or late and even become ulcerated; they are pathognomonic of congenital syphilis. With the involvement of one nail and a regional lymphadenitis, a primary lesion of acquired syphilis (A. Fournier's chancre panaris) should be considered; the importance of this is often undervalued.

B. Other and Late Forms.—In addition to the cutaneous manifestations, the mucous membranes play an important rôle. Coryza syphilitica is exceptionally important as an early symptom and not infrequently yields proof of spirochetes on dark-field examination. The characteristic "snuffles" of such infants are due to an edema with decreased secretion of the nasal mucous membranes, on which bloody and purulent scabs are also formed; these changes lay the foundation for deeper processes and later malformations of the nasal structure. Other mucous membranes, such as the conjunctivae, are less commonly involved, and sometimes contain spirochetes. Erosions and plaques appear at times in the buccal mucous membrane and can recur later. Rhagades at the angles of the mouth and on the tonsils, which at times are eroded and frequently contain spirochetes, should always be investigated. Experienced syphilologists, such as Hochsinger and others, emphasize the value of a hard enlargement of the cubital and thoracic (paramammillary) lymph glands.41 In addition to the hutchinsonian triad, Hochsinger considers a somewhat equivalent early triad of congenital syphilis, consisting of skull deformities (caput natiforme, saddle nose, etc.), radiating scars around the mouth (Parrot), and palpable cubital adenopathy. Gland puncture, which is so frequently practiced with acquired syphilis, seldom yields spirochetes in congenital syphilis. However, this practice should not be overlooked in ease of doubt.

Alopecia appears diffusely or in small patches, and the involvement of the eyebrows and cilia, as well as the scalp, is particularly characteristic; in older nursing infants and in small children it may be suggestive of syphilis acquisita infantum.

Especially after prenatal salvarsan therapy, superficial manifestations are frequently only minimal or may be absent. Because of this, syphilis congenita tarda may occur in which, after a more or less asymptomatic course, characteristic stigmas and involvements develop later. Besides the hutchinsonian triad of keratitis profunda, 2 nerve deafness, and typical alterations of the upper and middle incisors, as well as of the first molars, there are characteristic or suggestive signs (signs of certainty and probability of the French school), such as

<sup>&</sup>quot;I also advise examination of the lymph nodes in the axillae, etc.

<sup>&</sup>quot;For newer presentation, see Yokota (Zentraibl. f. Haut- u. Geschlechtskr. 51, 589).

widened knee joints, saber tibia (periostitis ossificans), changes of the ocular fundus (frequent, usually chorioretinitis), saddle nose, testicular atrophy, dwarfism or giantism, etc. The various tooth changes, which the young Fournier described in a very exaggerated manner as being produced by the syphilitic virus (microdontia, diastasis, hypoplasia of enamel, irregularity of form), have become much disputed since then. While definite signs are not known for the milk teeth, the real hutchinsonian tooth is typical of the permanent teeth, and is characterized by crescentic identation of the cutting edge, barrel or pear-shaped, screwdriver-like form, and frequently deviation of the converging axis. The collarlike atrophy of the first upper (six-year) molars is, to a certain extent, also characteristic, as well as the so-called Moon's tooth (better described by Pflüger). Other tooth changes should suggest a thorough examination for syphilis; they occur, however, in other morbid disturbances (idiocy, convulsions, etc.). Furthermore, the high arched palate may be mentioned here as a suggestive sign although this condition is more frequently a result of rachitis.

Besides megalosplenia and occasional enlargement of the liver, there are other symptoms in infants which are more or less suggestive: undernourishment, a peculiar pallor, no gain in weight or even a loss in spite of rich food, hydrocephalus, frequent vomiting and crying at night, nervous disturbances and convulsions (with striking venous dilatation, especially on the head). Nephrosis (albumin, edema) seldom occurs.

The manifestations of the so-called period of recurrences (second to fourth year of life), consisting of exuberant condylomas on the genitals and anus, alopecia microarcolaris, erosions of the mucous membranes, etc., in vigorous infants, should be considered as syphilis acquisita infantum. Some communications in the literature (chancres in ano and otherwise located extragenitally on the head and face, single or multiple) indicate how difficult the demonstration of chancres can be and how often they are not even considered. Acquired syphilis in infants usually does not run a severe course and, according to the opinions of experienced pediatricians, is rare compared with congenital (and binary) syphilis. This undervaluation of acquired forms of syphilis (condyloma, alopecia, etc.) is in need of revision, as I have often emphasized. It is known that children frequently run a lighter course with otherwise severe infections (e.g. typhus), and the same may commonly be true with syphilis.

C. Central Nervous System Disturbances (Spinal Fluid Changes) and Other Sequences.—Important as they may be for the physical and mental development of the child, endocrine dysfunctions and nervous system disturbances can only be mentioned briefly. Many cases of dystrophia adiposogenitalis, infantilism, dwarfism or gigantism, myx-

edema, eunuchoidism, contraction of the visual fields, diabetes, etc., have been explained on this basis, and in this case their treatment may become important.

With regard to the central nervous system, I may say that spinal fluid changes are common in early infancy, but are less frequently encountered later. This difference between early and late infancy may at times be explained by an early death of the severely infected infants, and by a spontaneous or therapeutically conditioned retrogression of spinal fluid syphilis as in acquired syphilis. A special form of spastic involvement is described by Marfan and is manifested in syphilis. addition to syphilitic meningitis, which can cause hydrocephalus, convulsions, and other signs (paresis, lameness, hemiplegia), there are other more or less obvious defects of the nervous system and disturbances of the intelligence, even to the point of idiocy. Late manifestations occur in the form of juvenile tabes and paresis<sup>43</sup> and become recognizable at the earliest in the fourth year of life; perhaps earlier spinal fluid examination would facilitate its diagnosis and treatment. Involvement of the vessels (arteritis or phlebitis in the brain and elsewhere) is also observed.

Gummas have been observed in all organs. Severe deep tertiary ulcerations often simulate lupus, etc., and can occur on the face, mouth, palate, nose (perforations), and other sites, causing deep ulceration and leaving as stigmas severe mutilating sears, often with bony involvement.

So much for the clinical manifestations, the polymorphism of which has not been completely discussed. When rachitis, tuberculosis, etc., develop along with congenital syphilis in infants, clinical pictures are observed which have given rise to the French theories of syphilis larvée. Here, however, there is the question of a combination of factors whereby in children, weakened through diaplacental infection, other diseases can occur more severely and in peculiar clinical forms. In these cases, specific therapy is often of striking benefit.

#### V. RECOGNITION AND EARLY DIAGNOSIS

Diagnosis, prognosis, therapy, and, finally, the social problem and prevention of congenital syphilis will now be briefly considered.

Of real help in the recognition of congenital syphilis are:

- 1. Carefully taken family history.
- 2. All methods of clinical investigation (inclusive of roentgenograms).
- 3. Investigation for the presence of spirochetes.
- 4. Serologic examinations.
- 5. Spinal fluid examinations.
- 6. Other methods (luctin reaction, blood sedimentation rate, etc.).

<sup>&</sup>quot;A large number of cases of juvenile neurosyphilis were recently reported by Menninger (Zentralbl. f. Haut- u. Geschlechtskr, 51, 680).

The importance of a thorough history, including that of the parents, siblings and nearer relatives, is universally admitted. It should include all suggestive symptoms (also stigmas) and the investigation of all suspects. French authors emphasize this especially; they have included investigation of all diseases which could be confused with syphilis, and properly so. Further, the history of births (abortion, premature, still-birth) is very significant, as has already been noted. The placenta, umbilical cord, and macerated fetus should always be thoroughly examined, because they can offer proof or arouse suspicion of congenital syphilis.

A. Obstetric Aspects.—An early obstetric diagnosis is extremely important. All pregnant women should be thoroughly investigated clinically after taking their history; but syphilis may be present in spite of negative findings. In addition, it is essential to make a serologic examination of all pregnant women, as far as possible in the fourth month (at the latest at the beginning of the fifth month), always using the standard methods (Wassermann reaction, Kahn test, Müller, Meinicke reaction, and also the sensitive Schreus-Wassermann reaction), which should be repeated in case of inconclusive results. Thus, patients with syphilis can be diagnosed in time for effective treatment to be instituted.

In addition to examination of the retroplacental blood, which seldom shows nonspecific reactions, the placenta and umbilical cord should be thoroughly examined (weight, placental quotient, macroscopic, and microscopic appearance). In all suggestive cases, a thorough search for spirochetes should be made by careful dark-field examinations (tissue scrapings from the vein walls of the fetal and placental ends of the umbilical cord); at times the silver staining of formalin-fixed sections will quickly reveal spirochetes (Armuzzi and others). For this purpose, the preservation of a 5 cm. length of the end of the umbilical cord is advisable, as I pointed out in 1928, for later demonstration of spirochetes by staining of sections. Employing silver stains, my students, Edm. Hofmann, Klaften, Philipp, and others, have frequently demonstrated spirochetes in the fetus and in newborn babies. When negative results are obtained from all of these methods, the investigation of the father and siblings at times may help the physician.

Many suggestions as to the clinical diagnosis have already been given. The differentiation of the simple pemphigus neonatorum (more superficial, noninfiltrated, paler lesions) from the syphiloid pyodermia on the buttocks, etc., is often possible by observation of the lesions, and can be proved by the finding of spirochetes. Although the serologic reactions are extremely important, they should be interpreted with caution during the first ten to fourteen days after birth. Instead of provocative reac-

tions in infants, I advise multiple tests and observations of the serologic curve, which does not decrease as rapidly in the presence of syphilis as it does in the case of false positive reactions.

B. Examination for Spirochetes.- Examination for spirochetes is still altogether too infrequent. India ink preparations (E. Müller and others), which pediatricians still use, are inadequate, being much too Repeated dark-field preparations of scrapings or tissue serum.44 which I have employed since 1905 with success, are always advisable since the demonstration of spirochetes on the first trial can be expected only when they are present in large numbers (Jahnel). In addition to vesicles and their floors, papules, erosions, rhagades, etc., the nasal and conjunctival mucous membranes are productive sites for scrapings. For the demonstration of spirochetes in adolescents and in children. I advise scrapings of the palatine tonsils, which frequently harbor spirochetes. In the newborn during the first nine months, no spirochetes can be found in the mouth (Erika Schneider, Eva Löb45). Scrapings and small pieces excised from portions of the skin (soles and heels) rich in spirochetes are often easier than obtaining preparations from the base of artificially produced vesicles (cantharides, carbon dioxide snow). For the early diagnosis of asymptomatic syphilis, the nasal mucosae and tonsils should always be thoroughly examined for Spirocheta pallida by repeated dark-field preparations. I have already stressed that by this method the diagnosis can be made immediately. while serologic examination requires one or more days. Therefore, the repetition of dark-field examinations is very important.

The luctin reaction is of little significance, and increased blood sedimentation rate is often suggestive but is not decisive.

C. Rocatgen Ray Procedures.—Roentgen ray examination of the epiphyses of the lower and upper extremities is very important for early diagnosis due to the frequent presence of Wegner's disease. Up to the third month it is pathognomonic; later, confusion may arise with rachitis, Möller-Barlow disease, etc. The essentials of Wegner's disease and of other forms (periostitis, etc.) have been stated previously. Many pediatricians consider roentgen ray examination very important, and this has been confirmed in Germany (Moro, etc.), as well as in France (Péhu).<sup>46</sup> It should always be employed, as well as spirochetal and serologic investigation, especially for the differentiation of congenital from acquired syphilis. At times, hutchinsonian teeth can be recognized in roentgen ray films before erupting through the alveolar ridges. (Stokes, Meyer-Buley<sup>47</sup>). Spinal fluid examination is also important

<sup>&</sup>quot;This alone made it possible for Schaudinn and myself to find Spirocheta pallida in 100 per cent of the cases, even in the serum obtained from lymph glands, in March and April, 1905.

Dissertation, Bonn, 1934. In collaboration with my student, Erika Schneider, Löb never found spirochetes in the tonsils or in the mouth before the ninth month.

<sup>&</sup>quot;Cervini and Bogani: Zentralbl. f. Haut- u. Geschlechtskr. 52, 330. Dissertation, Bonn, 1929, and Dermat, Ztschr. 58: 313.

and to be recommended in cases in which the diagnosis is in doubt. Transient or permanent spinal fluid changes occurring in infants suffice for the definite diagnosis of syphilis. The lumbar puncture is to be preferred to eisternal puncture in small children, the latter needing great skill.

D. Miscellaneous Facts.-In consequence of prenatal salvarsan therapy of most pregnant syphilities, the early recognition of congenital syphilis has become more difficult than formerly. It cannot be doubted that this sovereign therapy, as well as bismuth, is transmitted to the fetus through the placenta in efficacious form, and thus controls or produces a latency of the infection in the fetus. Whether a complete cure or an asymptomatic congenital syphilis results is very difficult to say. Symptoms, or positive serologic (and spinal fluid) reactions, can be absent up to the third or, at times, even to the fifth or sixth month. An examination three months after birth, which many believe to be sufficient, does not suffice for the exclusion of a congenital infection; it is much more practical to demand a follow-up of six months. Infants with normal placental quotients and negative spirochetal findings, who are entirely normal clinically, also should have this supervision if they are born of mothers who have had syphilis or are still syphilitic, even when a sufficient guarantee of cure seems certain due to intensive treatment before or during pregnancy.

Consideration of all of the above mentioned clinical symptoms (lymphadenopathy, splenomegaly, etc.) is again advised. The significance of the stigmas (Hutchinson, Fournier) has already been stressed. Spinal fluid examination is necessary in all nervous disturbances of childhood.

### VI. PREVENTION AND TREATMENT

Preventive measures and treatment, as already stated, have produced striking results. In order to reduce the incidence of congenital syphilis, there are two means at our disposal: specific therapy, which has long been well developed and has recently been simplified, and a far-sighted prophylaxis of syphilis in general. This may necessitate making exception to the otherwise valid rule: "Never institute specific therapy without a definite diagnosis."

A. Preventive Measures of Familial Syphilis.—The pregnant woman is the sole carrier of the causal agent of congenital syphilis and then only after the fifth month of pregnancy. This is the basis upon which we can and must work for the elimination of congenital syphilis. Because of confused and groundless theories of congenital syphilis ("germinative transmission" and "influence on the germ plasm, i.e., heredity"), the progress made has not been sufficiently great for an effective battle against it. When I presented my above mentioned articles in 1928-29, I tried to show the value of this fact.

The pregnant woman is also the starting point for our measures to reduce syphilis as a generalized affliction. She calls on the physician for other conditions and often for prenatal care. The axiom is then valid: "Always consider syphilis, as well as tuberculosis and cancer." There are social and charitable facilities for the care of pregnant women. Would it not be possible to examine every gravid patient for syphilis before the fifth month of pregnancy, without arousing suspicion? The family physicians of those who do not attend social clinics could also make a fundamental advance, for the sake of healthy future generations, by discreetly conducting a clinical and serologic examination. Thus, all syphilitic women—or almost all—could be reached at the opportune time and the birth of healthy children could be assured.

However, our efforts must extend still further, namely, to the prevention of infection of the mother by the syphilitic father, thus avoiding the introduction of infection into the family, with consequent prevention of familial syphilis in general. Today the attainment of this goal is not so difficult, because salvarsan in sufficient dosage quickly and efficiently checks the spirochetes which migrate to the surface and are thus capable of transmitting the disease. This rapid reduction of the danger of inoculation is also important for the reduction of familial syphilis, because infected men, with recently acquired syphilis, who allow themselves to be treated immediately, usually do not transmit their infection, even during treatment. I advise immediate treatment for women who have been exposed and probably infected by husbands whose syphilis is still infectious, even if proof of the spirochete is not found either in a cervical smear or elsewhere (urethra, tonsils, etc.). these possible, indeed probable, infections of short duration, the preventive treatment of one or two courses with short rest periods will suffice, provided that the serologic reaction remains negative on repeated examinations. Thus, the danger of familial syphilis is banished, and the possibility of congenitally syphilitic offspring is eliminated.

However, if that is not feasible, there remains the possibility of accomplishing not only the healing of the gravid mother, but also the birth of a healthy child by means of treatment during pregnancy. Our three-course system (Bonn) suffices for a final cure of early syphilis if it is not too old and unusually stubborn, which, however, our experience seldom shows to be the case. I emphasize again, along with experienced obstetricians, that this treatment, instituted early enough in the second half of pregnancy, should continue until parturition. in order to avoid danger of premature termination. A new course of treatment is not necessary in later pregnancy in women who have been treated intensively and systematically and whose cure may be assumed with sufficient probability. In my article, "Is Syphilis Curable?"

<sup>&</sup>quot;Ist Syphilis heilbar" Dermat. Ztschr. 59: 279, 1930.

I have explained the signs which are to be considered as indicating cure and a sufficiency of treatment; the publications of Zieler<sup>49</sup> may also be referred to in this connection.

A further simple measure for the prevention of familial and congenital syphilis is to advise the use of accepted methods of venereal prophylaxis by husbands who indulge in extramarital relations. Also, anticonceptional prophylaxis is to be recommended, that is, the conscious avoidance of impregnating syphilitic women until they have been sufficiently treated. If, in spite of this, pregnancy ensues before complete cure appears to have been accomplished, the prenatal treatment advocated under all circumstances by so many obstetricians must be carried out through the period of pregnancy, in order to ensure the birth of a healthy child.

B. Prenatal and Preventive Treatment—It has been our experience in general that two combined courses with a four-week rest period suffice for the prenatal treatment of the fetus, even in the presence of obvious syphilis. The assumption that gravid women after an initial dose of 0.3 gm. cannot tolerate individual doses of 0.45 gm. of neo-arsphenamine twice a week (thus 0.9 gm. weekly doses) is not in accordance with our long years of experience. Ten or, better still, twelve injections combined with bismuth constitute a course. Even larger doses of neosalvarsan (0.52 and 0.6) have been given to vigorous pregnant women in my clinic without any disturbance. The normal dose of 0.45 gm twice weekly ordinarily suffices to safeguard the fetus.

Frequently the mother as well as the child cannot receive this complete course during pregnancy, and are thus undertreated. These partially treated mothers and newborn babies must receive further therapy until the entire course has been given.

That leads us to the question which I brought up years ago, as to whether a preventive treatment of the newborn is advisable before the syphilitic infection can be definitely demonstrated. I have affirmed this for a long time and have found much support. Today, since the prenatal treatment has been further extended, a preventive treatment, representing only a continuation of that instituted prenatally, may be required. After the delivery, the mother and child are in the hands of the physician and, with sufficient explanations, should be amenable to proposals for therapy; later, it is more difficult to persuade the mother to continue treatment. Valuable time is lost and the chance of an early cure is decreased<sup>51</sup> with expectant observation. The damage which can occur from too intensive treatment is slight; much greater is the danger of further involvement which requires difficult and pro-

<sup>\*</sup>International Derm Congress Pudapost 1935

Pin mins (duntries (Japan, Jasa) the tolerance seems to be less (German prepara-

<sup>\*</sup>The publications of the Spiethoff clinic do not after this standpoint the customary treatment of silvars in ilternating with other preparations is the base of the Bonn system which has also been accepted in Denmark, Austria, Spain, etc.

tracted treatment, and which can have further sequelae, while the prognosis becomes poorer the longer one waits. A six-month observation period, therefore, is necessary in order to ascertain freedom from syphilitic involvement.<sup>52</sup>

That is basis enough to justify the preventive treatment of all newborn children of mothers who are still infectious or in whom infection is suspected. This should begin immediately after birth, if they have received inadequate, or no prenatal therapy. This standpoint is well grounded, because it offers the most for individuals and family, as well as for social-hygienic indications, and would contribute efficiently to the limitation of syphilis. Much care and expense is saved by such a procedure. Finally, babies, in whom the presence of syphilis is not definitely established, withstand antisyphilitic treatment very well, according to our experience. Against the advantages enumerated, a few really healthy infants will be treated. Their number will weigh slightly with most experienced physicians; furthermore, simple stovarsol therapy is regarded as sufficient by many clinicians.

C. Postnatal Therapy.—While I have seen good results from combined neosalvarsan-bismuth (or mercury) therapy with medium dosage (.01 gm. neosalvarsan per kilogram), recently stovarsal<sup>53</sup> treatment has been preferred by most pediatricians, gynecologists, and dermatologists and has been regarded as sufficiently efficacious. An intensive ninety-four-day course has been advocated by E. Müller, after he had previously—like myself—interceded for a very intensive combined calomel-neosalvarsan therapy. Also, I have employed the stovarsol therapy occasionally usually, however, with bismuth injections (0.002 to 0.003 gm. metallic bismuth per kilogram) or mercury inunctions. Details are given in my textbook of dermatology.<sup>54</sup>

E. Müller advises stovarsol therapy alone with large doses for ten days with four-day rest periods between (first dose,  $\frac{1}{2}$  tablet of 0.25 gm.; with vigorous infants, 1 tablet, and then a rapid increase to 2, 3, or 4 tablets daily). With a course of  $7 \times 10 = 70$  treatment days and  $6 \times 4 = 24$  rest days between, he tries to give 40-60 gm. of stovarsol and thus conclude the treatment in ninety-four days. With this treatment, the children become and remain healthy and serologically negative.

Other noted pediatricians advise beginning with small doses, then increasing slowly from 1/4 to 1/2, 3/4, and 1 tablet of 0.25 gm. in order to employ larger doses, according to tolerance, after the second or

<sup>\*</sup>Recently, Coppolino advanced the opposite view, that children, who presented no clinical, serological and roentgen findings one month after birth, did not require treatment. (Zentr. Bl. Hautkr. 52, 63).

<sup>&</sup>quot;No. 594 of Ehrlich's series is called spirozid in Germany, stovarsol in France, and acetarsone by the American Medical Association's "New and Non-Official Remedies." The tablet is 0.25 gm. by weight (translator's note).

<sup>\*</sup>E. Hoffmann: Behandlung der Haut- und Geschlechtskrankheiten, ed. 5, 1930. new edition in preparation.

third weeks; many combine this with mercury inunctions (0.1 gm. of 33 per cent ointment per kilogram) or bismuth injections. The total of the stovarsol—with or without short rest periods—amounts to from 24 to 30 gm.; by repetition of this course during the first half-year twice, and in later months even three times, this total can be reached.

Tolerance is usually high with good care and nourishment (as far as possible with mother's milk) and dosage suitable to the individual case; complications, such as vomiting, diarrhea, and exanthemas, are rare and can be controlled by suitable means (sodium thiosulphate). Severely involved newborn and infants occasionally die sooner, due to too intensive specific therapy (spirochetal toxicity), which deaths are no great misfortune since the infants would probably be backward physically and mentally. Preliminary small doses of mercury protiodide or several mercury inunctions and cautious stovarsol doses are suggested. Heavily infected infants, and preferably all, should at first be treated in hospitals. After retrogression of symptoms, and provided there is good tolerance, the simple stovarsol therapy can be continued as an out-patient treatment.

Stovarsol is not sufficiently efficacious for the prenatal treatment of pregnant women and is, therefore, no more permissible than malaria therapy during gravidity (transmission of plasmodia).

According to most experienced syphilologists, intensive stovarsol therapy, with dosage and duration adapted to the severity of the congenital syphilis, is very effective and so efficacious that neither recurrences nor nervous involvements ensue. Mental deficiency due to severe fetal infection cannot always be prevented, 55 but sufficient prenatal neosalvarsan and bismuth therapy must be given in order to make this prevention possible. Older infants and small children, as well as adults, should be treated by neosalvarsan (0.01 per kilogram) and bismuth as outlined in my book. In cases in which stovarsol is not sufficient, this treatment is to be advised and may be repeated once or twice, according to indications. The saturation therapy of Schreus or, better still, malaria followed by the Bonn method of therapy, should be considered.

Minor late involvements of other types do not always require intensive salvarsan-bismuth therapy; here, iodine and bismuth therapy suffice, especially if it is a quiescent noninfectious process or a benignappearing latent process (positive serologic reaction).

One more word about the intensity of the treatment. We have already mentioned that congenital syphilis shows a characteristic tendency toward spontaneous healing; thus, spinal fluid changes and visceral processes, with the exception of the bony involvement of Wegner, often disappear entirely, or to a large extent. It remains undecided whether, as a consequence of the growth process, infants and small children

ERecently, Kis and Rajka advised stovarsol therapy immediately after birth for all children of syphilitic parents, especially as a means of preventing defective intelligence.

possess a particular resistance to agents of infection, such as the Spirocheta pallida, but syphilis acquisita seldom runs a serious course. At all events, an excessively large dosage of stovarsol and neosalvarsan does not appear necessary because here the aid of vis medicatrix naturae can perhaps be relied upon. Therefore, in spite of my inclination for the maximal dosage, I have usually avoided dosages of more than 0.01 gm. neosalvarsan per kilogram and have usually had success with these small doses. Large doses, approaching the limit of tolerance, are not necessary with stovarsol; indeed, the goal at which maximal therapy aims, namely, a complete cure in a limited time, need not be considered.

#### VII. CONCLUSIONS

Great advances, which justify further hopes, have undoubtedly been attained during thirty years of etiologic and twenty-five years of therapeutic investigation. The specter of "hereditary syphilis" and "hereditary dystrophies," as well as "hereditary corruption" has been banished.56 The pregnant woman has been recognized as the sole intermediary for the transmission of congenital syphilis. The danger of transmission of spirochetes to the fetus is first present during the fifth month of pregnancy. This is the definite basis upon which we can lead an effective battle. Through suitable medical and social care, we must succeed more and more in getting in contact with all syphilitic pregnant women before the fifth month. With two prenatal courses of treatment extending from the middle to the end of pregnancy, healthy children can be produced, who are, and remain, free from signs of mental and physical inferiority.57 Postnatal preventive therapy administered to apparently healthy children, born of infected or infectious mothers, is justifiable and later avoids much affliction and Postnatal therapy of infected children has been simplified by stovarsol therapy which, according to the opinion of experienced clinicians, is efficacious; I have had good and lasting results with it, when combined with bismuth (or mercury) and neosalvarsan therapy.

The introduction of syphilis into the home can best be precluded by the preventive treatment of women who have been exposed to it. Measures have been suggested for the treatment of the infected man before marriage, in order to avoid the misfortune of familial syphilis. After getting in touch with the syphilitic pregnant woman, by means of her history and family investigation, further infectious cases can be traced and treated. By this procedure, which has been supplemented

<sup>&</sup>quot;Husler has discussed, but leaves open, Lenz's question of whether treatment of the parents by lodides, mercury, and arsenicals could influence, by heredity, the progeny such an apprehension is as groundless as the presumption that syphilitic toxins could influence heredity

<sup>&</sup>quot;Husler (Ztschr f Kinderh. 43 575, 1927) has never found syphilis in the third generation. I allowed Feige to discuss this subject in his dissertation (Bonn 1917) a syphilitic blastophthoria was never evident, nor even surmised. The physical and mental condition of forty-two congenital syphilitic adults was found by Husler to be above the average.

in most civilized countries by the formation of regulatory laws for the control of venereal diseases, and by the sympathetic cooperation of gynecologists, dermatologists, and pediatricians, a further diminution must result in the incidence of congenital syphilis and of acquired syphilis.

The definite reduction of congenital syphilis, as shown by yearly census in Denmark,58 to about one-tenth the former number in twelve years, with elimination of stillbirths and severe forms of the disease, must be an inspiration to us to continue the eradication of this disease which was once so greatly feared. The Danish and German results have been attained with German salvarsan preparations, the efficacy of which has been proved in the Ehrlich Institute at Frankfort;59 I have no experience with other arsenobenzine products. As the elimination of leprosy was accomplished in civilized lands in the Middle Ages without a specific therapy, we may hope for a still greater success in the battle against syphilis, with the aid of our modern knowledge of early diagnosis and treatment. The marked decrease of congenital syphilis and the elimination of its severe forms give us great confidence that we are on the right path and will be victorious. This goal would be reached still more quickly if the intensive combined treatments with short rest periods, shown by statistics to be most effective, were universally60 employed and if preventive therapy were more accepted.

<sup>\*</sup>Lenstrup (Copenhagen) stated on the basis of 250 congenite! symbilitie (hildren that syphilis is not the cause of imbeelility; instead, it is due to be a linear types. Therefore, he proposed the sterilization of such individuals (Sixin Northern Congress of Pediatrics, August, 1934).

FI. Hoffmann, ther die zweckmäszicste Behandlung der Syphilis (Wien. klin. Weinschr. 1935, 1010). It remains to be decided whether the recently recommended solusalvarsan is as good as the standard neosalvarsan.

Particulars are given in the article mentioned in the preceding footnote (59).

# EDEMA ASSOCIATED WITH HYPOGENESIS OF SERUM PROTEINS AND ATROPHIC CHANGES IN THE LIVER

WITH STUDIES OF THE WATER AND MINERAL EXCHANGES

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RECENT advances in our knowledge concerning the physiologic mechanisms involved in the exchange of body fluids have greatly heightened our interest in cases of so-called "idiopathic edema." It is obvious from an examination of published case reports that a variety of etiologically unrelated clinical entities have inadvertently been grouped together under this general designation merely because the origin of the edema in each instance has been undetermined. As a tentative diagnosis, therefore, "idiopathic edema" simply signifies that all known causative factors, such as nephritis, nephrosis, circulatory insufficiency, inflammatory and allergic disorders, severe anemia, protein starvation and the excessive ingestion of sodium chloride and water, have been excluded.

The present report deals with a case falling into this general category, which was the first of its particular kind to be recorded, so far as we are aware. As indicated in the above title, the underlying pathogenesis of the edema in this instance involved a marked degree of hypoproteinemia believed to be due to a deficiency in the physiologic mechanism for fabricating serum proteins. The postmortem discovery of a peculiar zonal atrophy in the liver lobules suggests the likelihood that this was the responsible pathologic lesion. Since our preliminary presentation of this case,1 Myers and Taylor2 have reported interesting clinical studies on a man fifty-one years of age, who was likewise suffering from chronic hypoproteinemic edema apparently due to an inability to produce serum proteins at a normal rate. During the past few months we have had the opportunity to observe an additional child presenting a somewhat similar clinical picture. It is not unreasonable, therefore, to believe that this entity will be recognized with increasing frequency, if searched for among the assortment of cases ordinarily classified under the designation, "idiopathic edema."

#### CLINICAL FEATURES OF CASE

The patient, E. N., was a girl two years of age, who was admitted to the Pediatric Service of the University of Minnesota Hospital on Oct. 5, 1931, because of intractable, generalized edema. According to her past history, she was delivered

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at term, weighing 9 pounds. Labor was "dry" and was prolonged to thirty-six hours. The face was observed to be swollen at the time of birth. This did not persist, however, and so was in all probability merely a result of difficult labor. Her early infancy was not remarkable except for frequent attacks of coryza. She was fed at the breast for nine months but was given cow's milk in addition after the first month. Cod liver oil and orange juice were given regularly after the first few weeks of life, and cereals and vegetables were added after the fifth month. After she was weaned from the breast, standard diets appropriate for the age were given. It is worthy of special note that her feeding and general care were under the supervision of a competent pediatrician throughout her entire life before she was

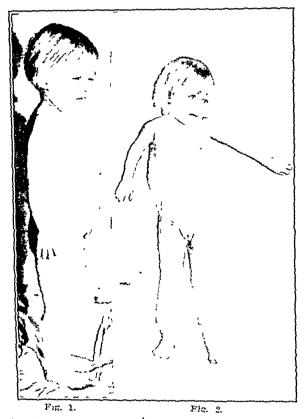


Fig. 1—Showing persistence of edema nearly five months after admission to the hospital in spite of high-protein, "salt-free" diet.

Fig. 2—Appearance of patient after loss of edema and ascites as a result of blood transfusion

referred to us for special study and treatment. Her development and growth were essentially normal. She walked at fourteen months and learned to talk shortly thereafter. She perspired unusually freely and always tended to be somewhat constipated. In all other respects she seemed to be essentially normal up to time of the present illness. The family history was not remarkable. Her parents, who were of Bohemian extraction, were both fairly healthy. She had no brothers or sisters.

Present Illness.—Edenia of the face and extremities sufficiently marked to attract the attention of her parents first appeared in January, 1931, following a "cold." This edema persisted without much change until March, when it ap-

parently subsided partially during an attack of whooping cough. Soon thereafter, however, it recurred and by July had become fairly marked. In September it was observed that the abdomen had enlarged considerably and the edema of the face and extremities had become still more conspicuous. Because of increasing irritability and abdominal discomfort, the patient was admitted to the University Hospital for more intensive study and treatment.

It is worthy of special emphasis that her diet had always been adequate as regards its protein and vitamin content. At no time was there any demonstrable evidence of cardiac, renal, or hepatic disease. Shortly after the first appearance of edema, when the patient was but fourteen months of age, the urine was examined carefully for albumin, casts and blood cells, but no abnormalities were found. Repeated examinations thereafter likewise yielded negative results.

On admission the patient appeared very much as she did when the photograph shown in Fig. 1 was taken. The general physical examination was essentially negative except for the obvious edema and abdominal enlargement. The edema was generalized but was more in evidence over the face and extremities than elsewhere. Protrusion of the abdomen was clearly due to the presence of freely shifting fluid. The texture and color of the skin and mucous membranes were essentially normal. The tongue was not enlarged. The hair was normal in amount, texture, and distribution. Except for fairly marked edema of the eyelids and slight hypertrophy of the tonsils, the eye, ear, nose, and mouth examinations were negative. Temperature was normal. Heart: Size, action, sounds and response to effort were entirely normal. Systolic blood pressure was 106 and diastolic, 72. Eyegrounds appeared normal. Lungs were clear. Nervous reflexes were all normal. X-ray examinations of the wrists, arms and legs showed her bone development to be normal. The urinary tract showed no abnormality by x-ray. The urine was negative for albumin, casts, blood cells, and glucose. Specific gravity ranged between 1.010 and 1.030. Phenolsulphonephthalein test showed 50 per cent exerction in two hours on one occasion and 60 per cent on another. Blood Findings: The Wassermann test was negative; nonprotein nitrogen 22.5 mg. per 100 c.c. The serum proteins were: albumin 1.9 per cent, globulin 1.5 per cent, total protein 3.4 per cent; plasma cholesterol 226 mg. per 100 c.c.; plasma chloride 357 mg. per 100 c.c.; serum calcium 11.25 and inorganic phosphorus 5.58 mg. per 100 c.c. Unfortunately fibringen was not determined, but the coagulation of the blood appeared to be entirely normal. Blood counts were as follows: erythrocytes, 4,480,000 per c.mm.; hemoglobin, 87 per cent; total leucocytes, 8,300 per c.mm. with 78 per cent polymorphonuclears, 17 per cent lymphocytes, 4 per cent cosinophiles and 1 per cent large mononuclears. Platelet counts were not made.

Clinical Course.—Because of the intractable nature of the edema and because her home lacked facilities adequate for her care, the patient was kept in the hospital for a period of 201 days, during which the special studies reported here were carried out. The urine remained albuminfree throughout this entire period except for a trace found in a single

sample at the height of her terminal infection. Except for a brief period following blood transfusion, the edema persisted in spite of a high-protein, low-salt, vitamin-rich diet and a constantly positive nitrogen balance. During the greater part of this period, she consumed daily between 2.5 and 3.5 gm. of protein per kilogram of body weight. Variations in the degree of edema occurred as a result of special procedures being tested, but none of the latter appeared to stimulate regeneration of the serum proteins. That the edema was due to a reduction in the colloidal osmotic pressure of the blood incident to marked hypoproteinemia was proved by its complete disappearance following blood transfusion, which raised the serum proteins above the critical level. Figure 2 shows the patient several days after the transfusion, when no edema was demonstrable. After a remission of a few weeks' duration, she again showed a

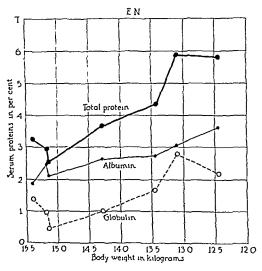


Fig. 3.—Showing inverse relationship between concentration of scrum proteins and degree of edema, as indicated by changes in body weight.

gradual gain in weight due to retention of fluid. After the edema had become apparent at the end of seven weeks, it was discovered that the serum proteins had again declined toward the original low level. At no time did the serum globulin fraction exceed the albumin in amount. The close relationship between the serum proteins and the degree of edema, as indicated by changes in body weight, is shown in Fig. 3.

# WATER AND MINERAL EXCHANGES

Obscurity regarding the underlying pathogenesis of this unusual form of hypoproteinemic edema suggested the desirability of measuring the water and mineral exchanges under a variety of conditions. The individual effects of parathyroid extract, of posterior pituitary extract, and of blood transfusion are shown in the accompanying charts, which are largely self-explanatory.

The methods used for measuring the water balance were those which we have employed in previously reported studies.<sup>3</sup> In brief they were as follows: The patient was kept in a special metabolism room in which the temperature was maintained between 67 and 74° F. and the relative humidity between 40 and 60 per cent at all times. A specially trained nurse supervised the administration of all food, drink, and medication, collected excreta, checked the room conditions and weighed the patient on a Troemner balance. During periods of special study the daily diet, which was given in four equal meals at six-hour intervals, was made up of powdered whole milk, egg yolk, egg white, cane sugar, clear lemon juice, and water. At other times the patient was given in addition meats, vegetables, fruits, yeast, and cod liver oil. Stools were separated by means of carmine given at the beginning of each period. They were dried to determine the water content. The

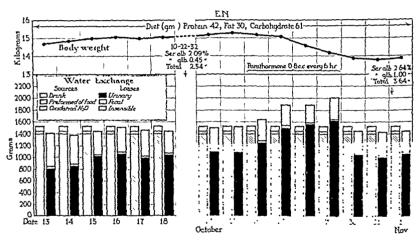


Fig. 4.—Partition of water exchange before and during administration of parathyroid extract. The latter is seen to cause a moderate reduction in edema in spite of low serum protein concentration.

insensible water loss of the body was calculated from body weight changes and a rough estimate of the metabolic mixture according to the method of Newburgh, Johnston, and Falcon-Lesses.<sup>4</sup> Serum proteins were determined according to the procedure of Howe as modified by Hawk and Bergeim.<sup>5</sup> The methods used for determination of the various minerals of the urine and stools were as follows: Sodium, Butler and Tuthill<sup>6</sup>; potassium, Shohl and Bennett<sup>7</sup>; chloride, Volhardt, as modified by Harvey<sup>8</sup>; phosphorus, Fiske and Subbarow<sup>9</sup>; calcium, Tisdall and Kramer<sup>10</sup>; and nitrogen, Kjeldahl.<sup>11</sup>

The data presented in the first part of the chart shown in Fig. 4 are typical of the water balance throughout the greater part of the patient's sojourn in the hospital. The measurements recorded are presented merely as a sample to illustrate the fact that edema persisted in spite of a "salt-free," relatively high-protein diet. It will be observed that

the total serum protein was barely half the value usually cited as approximating the critical level below which edema develops. In contrast to the reversal of the albumin-globulin ratio, which is characteristic of nephrosis, the globulin fraction was reduced to a greater degree than the albumin in this instance.

The effect of parathyroid extract (parathormone), as shown on the right half of the chart, was fairly effective in producing a negative water balance during the period of its administration. It is apparent that the negative balance was due exclusively to an increase in the urine volume. While the concentrations of both the albumin and the globulin of the serum were found to be somewhat increased following the period

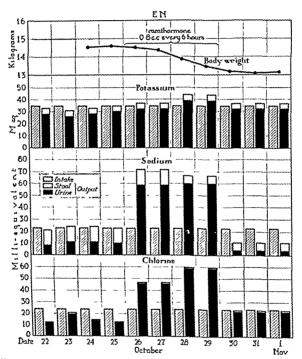


Fig. 5.—Effect of parathyroid extract on potassium, sodium and chlorine excretion.

of diuresis, they were not elevated above the "critical level" for edema formation. In fact, the extra water lost as a result of the administration of parathyroid extract was regained within a few days after withdrawal of the hormone.

In Fig. 5 are charted the intake and output of potassium, sodium, and chloride before, during, and after the period of parathyroid extract administration. That most of the edema fluid lost during the diuresis period was extracellular in origin is indicated by the excessive loss of sodium and chlorine. The slight negative balance of potassium during the third and fourth days may indicate a small loss of intracellular water during that portion of the period, but the amount is comparatively in-

significant. Following omission of the parathyroid extract, sodium began at once to show a positive balance, whereas the intake of chloride and potassium was equalled by the output. These observations merely indicate that the composition of the edema fluid in this case is essentially the same as that found in other forms of edema.

The effects of parathyroid extract on the calcium, the phosphorus, and the nitrogen balances are shown in Fig. 6. It will be seen that the nitrogen output remained unchanged. It is especially notable that the patient remained in positive nitrogen balance during the succeeding five months also, but failed to maintain her serum proteins at a level sufficiently high to prevent edema. The output of calcium and phosphorus by way of the kidneys and the intestines was significantly in-

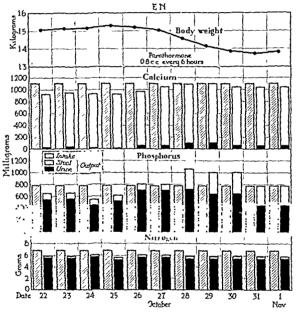


Fig. 6.-Effect of parathyroid extract on calcium, phosphorus and nitrogen balances.

creased by the hormone. Whereas the total calcium excretion had been definitely below the intake previously, the two were essentially equal during the parathormone period. The positive balance of phosphorus noted in the foreperiod was superceded by a definitely negative balance when the extract was administered. Unfortunately serum calcium and protein determinations were not made at the height of the period of diuresis and so it is impossible to say whether or not the degree of blood concentration was sufficient to explain the parathormone diuresis alone on an osmotic pressure basis. The nitrogen, the calcium, and the phosphorus excretion studies throw no light on this phase of the subject, but merely indicate that the patient's response to the extract was entirely normal as regards the calcium and phosphorus metabolism.

Because it had previously been found possible to cause loss of edema in certain cases of nephrosis by the administration and withdrawal of pitressin, the antidiuretic principle from the pituitary gland,<sup>3</sup> the procedure was carried out in the case of this patient. While she responded

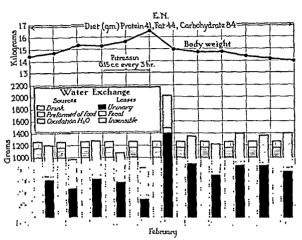


Fig. 7.—Effect of sustained pituitary antidiuresis and withdrawal on the water exchange.

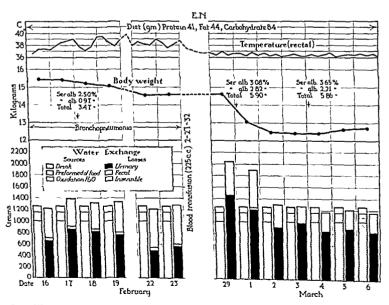


Fig. 8.—Effect of blood transfusion on the serum proteins and the water exchange.

Rapid loss of edema fluid.

to the sustained pituitary antidiuresis like other edematous subjects do, that is by a gain in body weight and an obvious increase in the degree of edema, her response to withdrawal of the hormone differed from that of the other patients mentioned in that the period of active diuresis was

not sufficiently prolonged to result in a significant net loss in body water. This failure was probably due to the fact that her serum proteins totalled less than 3.0 per cent at the time of the test.

The causative relationship between the depressed level of the serum proteins and the occurrence of edema is strikingly shown in Fig. 8. During the course of a mild attack of bronchopneumonia, the patient was given a fairly large transfusion of blood. Following a latent period of nearly two days, active diuresis set in. This resulted in a net loss of 2.3 kilograms of edema fluid within forty-eight hours. The total serum

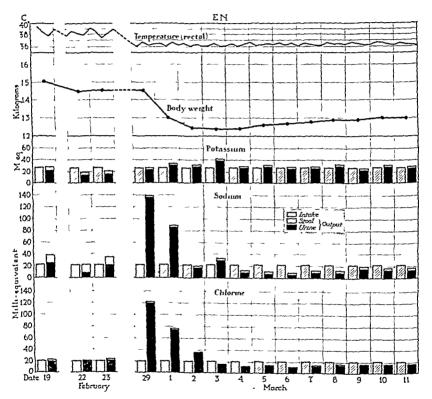


Fig. 9.—Potassium, sodium, and chlorine losses accompanying excretion of edema fluid after blood transfusion.

proteins were increased from approximately 3.5 to 5.9 per cent as a result of the transfusion. Since the serum protein value, 5.25 per cent + 0.25, may be regarded as the critical level below which edema develops, it is reasonable to assume that the elevation in serum protein level is alone sufficient to account for the result obtained. No adequate reason can be offered at the present time for the delay in appearance of diuresis following the transfusion.

It is obvious from the chart that practically all of the extra water lost was excreted by the kidneys. It will be observed that the amount

of water lost as insensible perspiration was significantly greater when the patient was edematous than it was after the edema had disappeared. Since the insensible water loss has been shown by Gilman and Barbour<sup>12</sup> to be inversely proportional to the osmotic pressure of the blood plasma, this observation might be interpreted as indicating a decrease in the value of the latter during the edema period, when the patient was on a low sodium chloride intake. The subject should be further investigated in patients with edema receiving various amounts of salt in the diet.

The mineral exchange data presented in Fig. 9 show that the water lost during the period of diuresis was derived from the extracellular fluid compartments of the body because the balances of sodium and chloride were strongly negative. In contrast the potassium balance

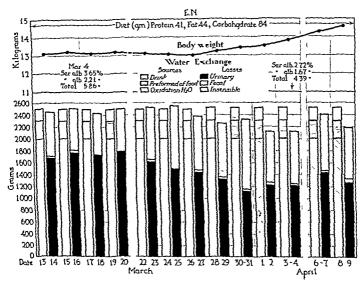


Fig. 10.—Water exchanges in posttransfusion period in two-day periods. Occurrences of edema associated with lowering of serum proteins in spite of high-protein diet

was but slightly altered. There was, nevertheless, a definite, though slight, increase in the exerction of potassium, which persisted well beyond the period of active diuresis. This might be interpreted as indicating a small outward shift of intracellular water.

Following a slight increase within a few days after cessation of diuresis, the body weight remained essentially stationary for approximately three weeks, as shown in Fig. 10. Thereafter, it rose gradually because of the recurrence of edema. Determination of the serum proteins after reappearance of edema showed their total value to have fallen somewhat below the accepted critical level for edema formation. The rather long period of freedom from edema following a single transfusion and the apparent gradualness of serum protein decrease suggest a slow

loss of the circulating serum proteins by ordinary "wear and tear" rather than by an active destructive process. Since the ascitic fluid present had but a low protein content and the urine contained no protein, it appears almost certain that the underlying defect lay in the patient's inability to form new serum protein molecules at a normal rate.

During her long period of hospitalization the general clinical picture remained essentially unchanged except for one mild attack of pneumonia, which she survived, and a later acute attack of unilateral otitis media with complicating mastoiditis. Following operation for the latter, the patient again developed bronchopneumonia from which she died on April 23, 1932. The total period covered by this latter episode was but a few days.



Fig. 11.—Section of the kidney. Note that the glomerulus and the tubules are entirely normal. Photomicrograph.

## POSTMORTEM EXAMINATION

Grossly the postmortem examination was negative, except for purulent exudate draining from the mastoid wound, early bronchopneumonia, and the presence of a moderate degree of generalized edema with excess of translucent fluid in the serous cavities. The heart was of normal size and development and appeared to be entirely free from acute and chronic disease. The hidneys were normal in size. The capsule was stripped from the cortex with ease, leaving a normal appearing surface. Microscopic sections (Fig. 11) showed that both tubules and glomeruli were entirely normal. The endothelial cells were small and inconspicuous, as they are normally in a child, and there was no thickening of the capillary basement membrane. The tubules contained no precipitated protein, and

the tubular cells were entirely normal in every respect. There was no evidence of disease in the interstitial structures.

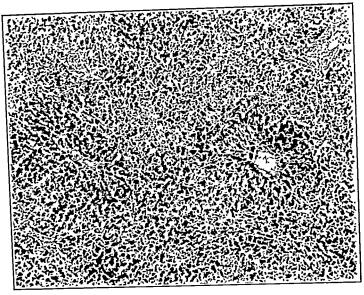


Fig. 12.—Section of the liver under low magnification. Note the persistence of the hepatic cords about the central veins and the extensive atrophy in other parts of the lobules. Photomicrograph.

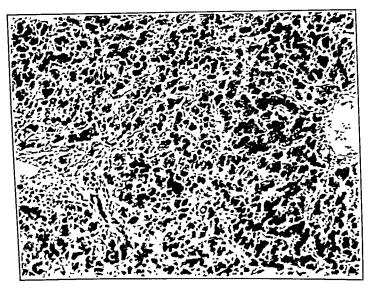


Fig. 13.—An area from Fig. 12 under moderate magnification. Note the preservation of the hepatic cords adjacent to the central vein (on the right side of the illustration) and the atrophy of the intermediate and peripheral zones of the lobule. Photomicrograph.

While the liver appeared normal macroscopically, a microscopic study revealed striking changes. Under low magnification (Fig. 12) a marked

atrophy of the hepatic cords, especially in the intermediate and peripheral zones of the lobules, could be seen. The hepatic cells about the central veins were usually intact. In Fig. 13 a part of a lobule is shown under higher magnification. The central vein is shown on the extreme right of the photomicrograph. The hepatic cords around the central vein were practically normal in appearance, while the cords in the intermediate and peripheral zones were broken and discontinuous. A portion of the atrophic zone of a lobule is shown in Fig. 14. It will be noted that the hepatic cords did not form a continuous network, an appearance evidently due to the complete degeneration and disappearance of adjacent cells. Fragments of necrotic cells could be seen, but there was no evidence of a diffuse necrosis of cells such as is seen in acute atrophy

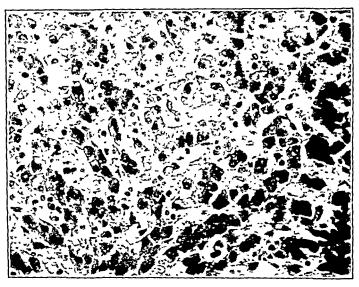


Fig. 14.—An area from the intermediate zone of a lobule under high magnification. Note the discontinuity of the hepatic cords due to the disappearance of a great many liver cells. Many cells are decreased in size and their surfaces are rounded because of absence of adjacent cells. Photomicrograph.

of the liver. The microscopic appearances were rather those of a chronic progressive atrophy of the hepatic cords. In some sections of the liver, lobules were found which showed instead of atrophy occasional small necrotic foci. The atrophy described above was, therefore, not uniform in degree throughout the liver. No explanation for the unusual lesion was found. It differed from the common forms of acute atrophy in the absence of extensive areas of nercosis. It was unlike subacute and chronic atrophy in that there was no cirrhosis. In states of prolonged severe malnutrition appearances similar to those in this case may occur. However, it is perhaps best to classify this disease as primary atrophy of the liver, i.e., one of undetermined etiology.

#### DISCUSSION

The features of special interest in the foregoing report are two: (1) that pertaining to the nature of the hypoproteinemia which was responsible for the edema and (2) that concerning the unusual pathologic lesions in the liver. Two unusual points regarding the serum proteins should be emphasized. The more important is that this patient manifested an unmistakable deficiency in her mechanism for fabricating these important blood constituents. This appears to us to be definitely proved by the fact that marked hypoproteinemia persisted over a period of many months in spite of a high-protein diet with constant maintenance of a strongly positive nitrogen balance. The proteins included in the diet were of good quality for serum protein regeneration, according to the recent work of Whipple and his coworkers12 on the comparative efficiency of different dietary proteins. It was satisfactorily determined that extra protein was not lost by way of the urine, feces, or ascitic and edema fluids. Abnormal destruction of serum proteins appears to have been ruled out by the fact that the descent of their levels following blood transfusion was extremely slow. The second unusual point is the symmetrical reduction in the serum albumin and globulin fractions. no time was the albumin-globulin ratio reversed. In fact, the regeneration of globulin appears to have been slightly more impaired than that of the albumin.

The characteristic lesion in the liver lobules was unique in that no true cirrhosis, no infiltration of wandering cells, and no necrotic cellular débris were apparent. Since the morphologic blood picture remained essentially normal and no other parenchymatous lesion than that in the liver was found, this observation appears to us to substantiate the theory of Whipple and coworkers<sup>14a</sup> and b that the liver is the chief site of formation of the serum proteins. The peculiar distribution of the lesions further suggests that this process may be a more or less specialized function of those cells situated in the intermediate and peripheral zones of the hepatic lobules.

The direct cause of the liver lesions is unknown. The early age of the patient at the onset of edema, the lack of any clear-cut history of preceding infection or intoxication and the small size of the hepatic cells might be interpreted as suggestive evidence of a congenital defect in the development of these structures, but no further proof of this somewhat fantastic explanation is available. It is of passing interest, however, that three years after the death of this patient, her parents brought a second child, eighteen months of age, to us with the complaint that she seemed at times to show slight edema similar to that shown by E. N. at the onset of her illness. No pitting edema could be demonstrated at the time of our examination, but her serum proteins as well as those of the parents were determined. From the point of view of heredity it may or may not be significant that this sister's total serum protein was

found to be but 6 per cent, and her father's but 6.12 per cent, while the mother's was 7.4 per cent. The parents were to report to us in case edema became apparent in this child. An additional year has passed, but no report has been received.

Various observers<sup>15, 16, 17, 18</sup> have reported a decrease in serum or plasma proteins in liver disease, particularly in cases of cirrhosis with ascites and edema. This has usually been attributed to underfeeding of protein in such cases, and the edema has often been referred to as being a result of cardiac insufficiency and venous obstruction. Myers and Keefer<sup>18</sup> found, however, that certain patients with severe cirrhosis lost significant amounts of protein into the ascitic fluid. They concluded that such patients probably suffer also from decreased ability to produce scrum proteins, particularly albumin. They, like other contributors to the subject, found the albumin-globulin ratio of the serum to be reversed in the majority of instances. The case reported here and that reported by Myers and Taylor<sup>2</sup> differ from cases of ordinary circhosis in that there was never any tendency to a reversal. These two patients showed a marked deficiency in their capacity to fabricate globulin as well as albumin. This deficiency was the primary factor in their abnormal retention of water. The ascites was a feature of the generalized edema, just as it is in the case of lipoid nephrosis. There was no evidence of venous obstruction or of cardiac or renal insufficiency.

#### SUMMARY AND CONCLUSIONS

- 1. Clinical and metabolic studies were carried out over a period of many months in the case of a patient suffering from "idiopathic" hypoproteinemic edema.
- 2. No evidence of cardiac or renal disease was obtained during her lifetime. The formed elements of the blood were repeatedly found to be entirely normal.
- 3. The low levels of the serum albumin and globulin were uninfluenced by high protein feeding, although a strongly positive nitrogen balance was known to be maintained thereby over a period of more than six months.
- 4. Since no other cause for the symmetrical lowering of the serum proteins could be found, it was assumed that the body's mechanism for their regeneration was defective.
- 5. Studies on the water and mineral exchanges showed the edema per se to differ in no essential way from that due to the hypoproteinemia of protein starvation or that due to excessive protein loss.
- 6. Elevation of the serum proteins by means of blood transfusion resulted in complete disappearance of the edema, demonstrating a direct relationship between the low serum proteins and edema formation.
- 7. Postmortem examination revealed a comparatively widespread atrophy of hepatic cells, which was confined chiefly to the intermediate

and peripheral areas of the liver lobules, the central zone being spared. No lesions were present in the kidneys, heart, or other parenchymatous organs.

- 8. In the light of these data the tentative conclusion has been drawn that this unusual liver lesion was responsible for hypogenesis of the serum proteins and consequently for the development of edema and ascites.
- 9. Hypoproteinemia in the absence of albuminuria and protein starvation should be regarded as at least presumptive evidence of one form of hepatic insufficiency.

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### TRAUMATIC PNEUMOTHORAX IN THE NEWBORN

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P NEUMOTHORAX is of uncommon occurrence in children. Scott<sup>1</sup> in 1928 collected 177 cases in children of various ages. In reporting his own case of pneumothorax, Davies<sup>2</sup> reviewed twenty-seven previously reported. In 1931 Coccheri and Rossi<sup>3</sup> reported 300 cases from the literature dating from 1844 to 1930, including sixteen cases of their own.

Stoloff' is of the opinion that tuberculosis is probably the most frequent single cause of pneumothorax in children. On the other hand, according to Anderson and Catheart<sup>5</sup> tuberculosis as an etiologic factor is rare as compared to the 3 per cent occurrence in pulmonary tuberculosis in adults. However, in considering the nontuberculous causes of pneumothorax in infants and children, Lereboulet and his associates6 and Royer de Véricourt7 list pneumonia, empyema, lung abscess, and pertussis as the most frequent. Cases of spontaneous pneumothorax either accompanying or following pneumonia have been reported by Bashinski, Lacchia, Acuna and his coworkers ond others. 11, 12, 13 In reporting a case of pyopneumothorax from our service, Rogatz and Rosenberg14 found only twelve similar cases in the literature occurring during the first year of life. Direct trauma to the chest (Macera and Perissé<sup>15</sup>) or prolonged difficult deliveries (Donahoe<sup>16</sup>) may also cause pneumothorax. Pissavy and Zimmer<sup>17</sup> report a case of pneumothorax following puncture of the pleura in a fifteen-year-old child. Ruge18 in 1878 described the first case of pneumothorax in the newborn. In 1930 Stein.19 in a report with a review of the literature, described four cases and added one of his own. Gasul and Singer<sup>20</sup> brought the series up to eight cases. In an excellent monograph, Glaser and Landau<sup>21</sup> reported seventeen cases, including one of their own, with a mortality of 47 per cent in pneumothorax in the newborn. Flipse22 is the only author to report a case of pneumothorax following hypodermic medication. The following report of a case of pneumothorax in the newborn is of interest because we were unable to find in the literature a report of a similar case caused by attempted cardiac puncture.

From the Abraham Jacobi Division for Children of the Lenox Hill Hospital, New York, Service of Dr. Jerome S. Leopold.

#### CASE REPORT

### (Courtesy of Dr. Arthur Stein)

H. P. H., male, newborn infant, was born by a precipitous delivery on Dec. 2, 1935, ten hours after the onset of labor. The birth weight was 5 pounds 81/2 ounces.



Fig. 1.—Showing a 50 per cent pneumothorax, partial collapse of the left lung, and shifting of the mediastinum to the right.

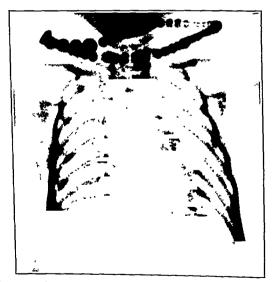


Fig. 2.—Showing complete absorption of the air, with the mediastinum normally located.

At birth the infant appeared very pale, listless, and did not breathe. In attempts at resuscitation, besides immersion in hot and cold water tubs, alternately, and dilatation of the rectum, one ampule of medication was injected supposedly into the heart

by means of a 24 gauge, 34 inch needle. When a weak cry was heard, the infant was at once placed in an incubator and oxygen was administered continuously. Complete physical examination several hours later revealed the following findings:

The infant appeared apathetic and somewhat cyanosed. Stimulation produced a very weak cry. The respirations were rapid and shallow. The skin was pale and dry. The mucous membranes and the extremities were slightly cyanotic. The anterior fontanel was patent, of normal fullness, and admitted two fingers. The neck was normal. On the chest wall, a needle puncture wound was present in the third intercostal space, just to the left of the sternum. On the left side the thorax appeared fuller than on the right. The respiratory excursions were markedly diminished; tactile fremitus was practically absent; percussion produced a tympanitic note. The breath sounds were exaggerated over the entire right side, and were markedly diminished over the left chest. No râles were heard. The heart sounds were heard best to the right of the sternum. The abdomen was soft. The liver edge was easily palpated just below the right costal margin. The spleen was not felt. The genitals and extremities were negative. A diagnosis of left-sided pneumothorax was made and was confirmed by roentgen ray examination (Fig. 1). During the first thirty-six hours of life, the infant had four stools consisting of meconium and mucus streaked with fresh blood. The blood was explained on the basis of the trauma to the anus produced secondary to the dilatation procedure instituted as a stimulating measure at birth. The infant was kept in the incubator, and oxygen was administered continuously. The physical findings improved daily. It was noted that the point of maximum intensity of the heart sounds was steadily shifting from the right of the sternum to the left. The breath sounds on the left side gradually became normal.

On Dec. 9, 1935 (7 days after birth), the physical examination of the chest was entirely normal. Roentgen ray examination (Fig. 2) revealed complete disappearance of the pneumothorax. The oxygen was discontinued. The stools had become free of blood, and the infant was taking breast milk with a complementary formula satisfactorily. When discharged from the hospital on Dec. 11, 1935, the infant weighed 5 pounds 6½ ounces. When seen at the age of five months, he weighed 14½ pounds, was 25¾ inches long, and had two teeth. The infant was of normal development and well nourished.

#### DISCUSSION

In reviewing the literature on pneumothorax in the newborn, the explanation most frequently advanced for the mechanism of production is the rupture of an alveolus during resuscitation causing a bronchopleural fistula. Flipse<sup>22</sup> feels that forceful respiratory movements at the onset of respiration in his case were caused by an aplasia of the epiglottic cartilage with subsequent collapse obstructing the glottis. In Stein's<sup>19</sup> case there was apparently a permanent bronchial communication with the pleural cavity because at the end of two years no expansion of the right lung had occurred. In the case presented by Gasul and Singer,<sup>20</sup> the pathogenesis was described on the basis of aspiration of infected material at birth with the production of a localized pneumonitis. This process, going on to abscess formation, ruptured at the age of three weeks, causing pyopneumothorax and leading to death in three days. In the case reported by us, it is felt that

air entered the pleural cavity through the needle puncture wound during the first few respiratory efforts. With the onset of the respiratory movements and the subsequent production of a negative pressure in the pleural cavity, air was most likely sucked in through the puncture wound. This readily explains the rapid clearing up of the pneumothorax within seven days.

#### SUMMARY

A case of a newborn infant is presented in whom pneumothorax developed apparently secondary to puncture of the left chest. air was spontaneously absorbed within seven days. Complete recoverv resulted.

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- - 26 EAST 63RD STREET
  - 2 EAST 54TH STREET

# THE BACTERIAL FLORA OF MECONIUM SPECIMENS COLLECTED FROM SIXTY-FOUR INFANTS WITHIN FOUR-HOURS AFTER DELIVERY

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In HIS dissertation of 1886 Escherich<sup>1</sup> stated that the meconium of the infant was sterile and bacteria did not appear until four hours after birth in the summer and seventeen hours in the winter. Subsequent workers, Schild,<sup>2</sup> Szego,<sup>3</sup> Sittler,<sup>4</sup> Tissier,<sup>5</sup> Cruickshank and Cruickshank,<sup>6</sup> and Passini,<sup>5</sup> furnished data supporting Escherich. Statements to this effect may be found in the texts of Ford,<sup>8</sup> Topley and Wilson,<sup>9</sup> Zinsser and Bayne-Jones,<sup>10</sup> Park and Williams,<sup>11</sup> and Kendall.<sup>12</sup>

Exceptions to these findings, however, have been recorded which suggest strongly that bacteria may occasionally be present in the meconium at birth. Hymanson and Hertz<sup>13</sup> found bacteria in nine of thirty-nine meconium specimens collected by rectal swab shortly after birth and streaked out on serum glucose agar. Burrage<sup>14</sup> in 1927 reported the cultivation on solid media of bacteria from thirty-eight of one hundred first passage specimens of meconium, the first of which was collected at delivery and was found to contain many bacteria. A similar series of fifty first passage specimens was recorded in 1934 by Hall and O'Toole<sup>15</sup> who obtained the same percentage of positive results as Burrage. They used both solid and liquid media. In the last two instances most of the specimens were obtained from sterile diapers brought to the laboratory from the nursery. No attempt was made to collect the specimens regularly at or within a short time of delivery.

The present investigation undertook to determine the presence of bacteria in the intestinal contents at birth, as well as in the four-hour period following delivery. The mode of invasion was also considered.

#### METHODS OF COLLECTION AND EXAMINATION

The time of collection ranged from four minutes to three hours and ten minutes after delivery. A swab on a fairly stiff copper or iron wire which was placed in a short length of glass tubing was used to collect the specimens. This combination, with a small amount of easter oil for lubrication, was placed in a test tube and sterilized in the autoclave at fifteen pounds' pressure for one-half hour. Several tests showed the oil to be sterile. The anal region of each of the first few infants was sponged with Sharpe and Dohme S. T. 37, but this was

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discontinued because of its slow evaporation and 95 per cent alcohol was used for the remaining cases. A control test of this area was made by rubbing it with an ordinary swab which was placed in glucose broth. These control cultures showed that this method of sterilizing the anus and buttocks was not entirely efficacious, but no other satisfactory method was found. The meconium was collected by inserting the tube well past the anal sphincter, pushing the swab still farther into the rectum, and withdrawing the swab, which brought meconium into the tube.

The following technic was employed for examining the meconium. When the meconium was present in sufficient quantity, it was examined microscopically by cover slip as well as Gram's stain. The results of these examinations were invariably negative. A small amount of meconium was streaked across cosin methylene blue and blood agar plates to determine the presence of gram-negative and gram-positive aerobic organisms, respectively. An additional amount was placed in freshly boiled and cooled brain medium for the enrichment of what few bacteria might be present whether aerobic or anaerobic. In a few cases when brain broth was not available glucose broth was used. Occasionally the meconium was streaked out on blood agar slants which were made anaerobic under alkaline pyrogallol; these were all sterile.

#### RESULTS

To date, the meconium collected by this method within four hours after delivery was examined from sixty-four infants, including two of cesarean birth. These cases were divided in respect to time as follows: twenty-nine were collected within thirty minutes after delivery; ten between thirty minutes and one hour; sixteen between one and two hours; and nine between two hours and three hours and ten minutes.

The thirty-minute period was selected arbitrarily to cover as many cases as possible within a short time after the arrival of the baby. The babies who came within this limit, the organisms isolated, and the control cultures of the skin surface of the anal area are listed in Table I.

Table I shows that three out of twenty-nine specimens of meconium obtained within thirty minutes after delivery showed positive bacterial growth on streaked plates. That these organisms must have been present at birth in Case 6 seems indisputable, for the specimen was collected nine minutes after delivery, and there were numerous colonies along the streak on the blood agar plate. The failure of the *L. acidophilus* to grow in enrichment media cannot be explained. In Case 29, colonies appeared in large numbers along the streak on the blood agar plates. Among these were hemolytic colonies of *Streptococcus pyogenes* whose presence in a meconium specimen collected within a half-hour after delivery caused some concern for the mother, but nothing abnormal was recorded for the postpartum period of ten days in the hospital.

Str. mitis was also isolated from the plate, and both species of streptococcus and B. coli were recovered from the enrichment culture. In Case 27 there were only three colonies of B. coli at the beginning of

			RESULTS	
NO.	TIME*	PLATE	ENRICHMENT	SKIN CULTURES
1	4	Sterile	Sterile	Sterile
2	8	Sterile	Sterile	Sterile
3	8	Sterile	Sterile	Sterile
9 3 4 5 6	S   S   9	Sterile	Sterile	B. coli
5	9	Sterile	Sterile	M. epidermidis
6	9	L. acidophilus	Sterile	Sterile
7	10	Sterile	Sterile	Sterile
7 8 9	10	Sterile	Sterile	Sterile
9	10	Sterile	Sterile	Sterile
10	10	Sterile	Sterile	Sterile
11	10	Sterile	Sterile	Sterile
12	11	Sterile	Sterile	Sterile
13	} 22	Sterile	Sterile	Sterile
14	13	Sterile	B. coli	B. coli
15	13	Sterile	Bacteroides species	M. epidermidis
16	14	Sterile	Sterile	Sterile
17	14	Sterile	Sterile	Sterile
18	15	Sterile	Sterile	Sterile
19	15	Sterile	Bacteroides species	Sterile
20	16	Sterile	Sterile	Sterile
21	16	Sterile	M. aurantiacus	M. epidermidis
22	17	Sterile	Sterile	Sterile
23	18	Sterile	Sterile	Sterile
24	19	Sterile	Sterile	Str. mitis
25	20	Sterile	Sterile	Sterile
26	20	Sterile	Anaerobic coccus	Sterile
27	20	B. coli	B. coli	B. coli
	1		Str. fecalis	Str. fecalis
28	26	Sterile	Sterile	Sterile
29	30	Str. pyogenes	Str. pyogenes	Not taken
	}	Str. mitis	Str. mitis	1
	1	1	B. coli	}

<sup>\*</sup>Time in minutes from birth to collection of specimen.

TABLE II
SPECIMENS OF MECONIUM COLLECTED BETWEEN THIRTY AND SINTY
MINUTES AFTER DELIVERY

NO.	DELIVERY AND	RESULTS			
	COLLECTION	PLATE	ENRICHMENT	SKIN CULTURES	
1 2 3 4 5 6 7 8 9	31* 34 35 39* 52 55 57 59 59	Sterile	Sterile Sterile L. acidophilus Sterile Sterile Sterile Sterile Sterile B. coli M. cpidermidis B. coli C. hofmanni	Sterile Sterile M. epidermidis Sterile Sterile Sterile Sterile Sterile Sterile Sterile Sterile Sterile	

<sup>\*</sup>Cesarean birth.

the streak, but *B. coli* and *Str. fecalis* were isolated from the enrichment cultures as well as the skin area. Bacteria were demonstrated in five more of the specimens by enrichment procedures. The isolation of the unidentified species of the genus Bacteroides and the anaerobic coccus indicates the necessity for anaerobic methods in this type of study. The relation of the organisms isolated from the meconium and skin areas by enrichment is discussed later.

Specimens of meconium were collected from ten babies between thirty and sixty minutes after delivery; the results are summarized in Table II.

In the small series listed in Table II no bacteria were isolated directly, but in four of the ten specimens bacteria were shown to be present by enrichment methods. Only one control culture from the skin was positive for bacterial growth, and no duplication occurred with the corresponding culture of meconium in enrichment medium.

Sixteen specimens of meconium were collected between one and two hours after delivery; the results are recorded in Table III.

TABLE III

SPECIMENS OF MECONIUM COLLECTED BETWEEN ONE AND TWO HOURS
AFTER DELIVERY

	TIME BETWEEN	RESULTS			
NO.	BIRTH AND COLLECTION	PLATE	ENRICHMENT	SKIN CULTURES	
1	1:00	Sterile	C. hofmanni	Sterile	
	1:00	Sterile	M. albus	M. epidermidis	
2 3	1:03	Sterile	M. candidus	Sterile	
Ü	1.00	75101110	D. catarrhalis	Bierne	
4	1:04	Sterile	L. acidophilus	Not taken	
4 5 6 7	1:05	Sterile	B. coli	Sterile	
G	1:10	Sterile	Sterile	Sterile	
7	1:15	Sterile	B. welchii		
•	1.10	Sterne	C. hofmanni	Sterile	
	}		M. epidermidis	l l	
Q	1:15	Sterile	Sterile	· · · · · · · · · · · · · · · · · · ·	
8 9	1:15	Sterile	Sterile	Hay bacillus	
10	1:16	Sterile	Sterile	Not taken	
11	1:21	Sterile	r	Sterile	
11	1:41	Sterne	M. epidermidis	M. epidermidis	
12	1:30	Sterile	S. salivarius		
14	1:50	Sterne	B. coli	Sterile	
13	7.42	C6:1-	M. epidermidis	\	
10	1:43	Sterile	Sterile	M. epidermidis	
14	1:46	Sterile	Q1 - 12 -	Str. salivarius	
15			Sterile	Sterile	
19	1:53*	Sterile	Str. fecalis	Sterile	
10	1.50*		B. coli	1	
16	1:56*	Sterile	Str. fecalis	Sterile	
	I	1	B. coli	ĺ	

<sup>·</sup>Twins.

No bacteria were demonstrated by direct plating in any of the sixteen meconium specimens recorded in Table III. With enrichment media, however, ten of the sixteen specimens yielded positive results. This is a distinct increase in the positive results over those obtained

in the preceding time periods. The isolation of B. welchii, the one species of sporulating anacrobe encountered, indicates again the necessity of anacrobic methods.

Nine specimens were obtained between two hours and three hours and ten minutes after delivery. These are shown in Table IV.

TABLE IV

BACTERIAL PLORA OF SPECIMENS OF MECONIUM COLLECTED BETWEEN TWO
HOURS AND THREE HOURS AND TEN MINUTES AFTER DELIVERY

XO.	BIRTH AND	RESULTS				
••••	COLLECTION	PLATE	ENRICHMENT	SKIN CULTURES		
1	2:00	Sterile	M. aurantiacus	Sterile		
2	2:05	Sterile	Sterile	Sterile		
3	2:17	Sterile	Str. salivarius	Not taken		
4	2:25	Sterile	M. epidermidis	Sterile		
5	2:35	Sterile	M. albus	M. albus		
6	2:46	Sterile	M. epidermidis	Not taken		
7	3:00	L. acidophilus	M. candidus	Not taken		
	1	1	L. acidophilus	1		
8	3:03	Sterile	M. candidus	Sterile		
9	3:10	Sterile	Sterile	Sterile		

Table IV shows that in only one case were bacteria numerous enough to be demonstrated by direct plating, but nine of the ten specimens gave positive results with enrichment methods. Only one of seven control cultures from the skin was positive for bacterial growth; the same species, *M. albus*, was also isolated by enrichment from the corresponding meconium specimen.

The species isolated from the specimens of meconium from sixty-four newborn infants within four hours after delivery are summarized in Table V in respect to frequence, time intervals, and methods of isolation. The cultures from the skin tests are included for comparison.

Table V shows that only four species of bacteria were isolated by direct plating methods. These species included two strains of L. acidophilus and one each of B. coli, Str. pyogenes, and Str. mitis. Thirteen known species, two unidentified species of the genus Bacteroides, and one unidentified anaerobic coccus were isolated by enrichment methods. Their frequence is given: B. coli, nine times; M. epidermidis, six; L. acidophilus, four; C. hofmanni, Str. fecalis, and M. candidus, three; M. albus, M. aurantiacus, Str. salivarius, D. catarrhalis, and Bacteroides species, two; and Str. pyogenes, Str. mitis, B. welchii, and an unidentified anaerobic coccus, once each.

The bacteria recovered from the skin cultures were six strains of *M. epidermidis*, three of *B. coli*, and one each of *Str. mitis*, hay bacillus, *Str. feealis*, and *M. albus*,

#### DISCUSSION

Although specimens of meconium were obtained up to three hours and ten minutes after delivery, it was obvious that those collected as soon

Table V

13 ± 55 13.6 TOTAL  $\frac{1}{16.7}$ 3-4 нв. SKIN CULTURES 1.4 10 4 28.0 FREQUENCY OF BACTERIAL SPECIES IN SPECIMENS OF MECONIUM COLLECTED WITHIN FOUR HOURS AFTER DELIVERY 1-2 HR. 12.530 MIX.-1 HR. .zik 08-0|25 64 36 28 48.3 ÷ :: က 21 C.J 0 0 1 7 7 8.0 3-4 нв. UNRICHMENT METHODS 16 6 10 62.5 1-2 HR. 3.1 6 40.0 .an I .zik 08 52 .XIX 08-0 21X. ខ្លួន្ត្ 64 60 6.3 INTOI 1 ្នា .an 4-2 DIRECT PLATING 1-2 ик. 16 16 0 30 MIZ, I HR. 5000 05-0 MIX. Bacteroides species Annerobic cocens Str. salivarius
Str. fccalis
M. aurantiacus
D. catarrhalis M. epidermidis L. acidophilus Str. pyogenes Str. mitis B. welchii C. hofmann M. candidus Hay bacillus % Positive M. albus Specimens Negative Positive

as possible were of more value in answering the question whether bacteria are present in the meconium at birth. The most striking proof was the specific case where the collection was made nine minutes after delivery. Nothing had been done to the infant, such as washing or taking the rectal temperature. No organisms were isolated from the skin of the anal region by enrichment, but numerous delicate colonies appeared in from forty-eight to seventy-two hours along the streak on the blood agar plate inoculated with the meconium. These organisms were tentatively classified as Doederlein's bacillus or L. acidophilus, the identity of which was pointed out by Thomas<sup>16</sup> in 1928. The presence of such numbers of bacteria, even if not seen microscopically, would seem to be proof of their multiplication in the meconium before birth.

The relation of the bacteria isolated from the skin surface of the anal areas to those recovered from the meconium by enrichment methods warrants some consideration because it would seem that the isolation of organisms from the anal area might limit the value of the positive results obtained by enrichment of the respective meconium specimens. possibilities exist: First, when bacteria are isolated from the meconium and not from the anal area, it would indicate the presence of a few organisms in the meconium and either that cleansing of the skin of the anal region was satisfactory or that the surface was sterile at birth. Second, the culturing of bacteria from the skin and not the meconium suggests that although the cleansing was not completely efficient, organisms had not invaded the meconium. Third, isolation of the organisms from both skin and meconium may be interpreted in two ways. isolation of a species from the anal area unlike the species recovered from the meconium would not necessarily interfere with the assumption of bacterial growth from a few cells in the meconium. The isolation of the same species from both skin area and meconium, however, suggests either the occurrence of per anum invasion with natural duplication of results from these two sources or direct exterior contamination of the meconium specimen from the skin.

If the thirteen cases of positive skin cultures are analyzed in light of these possibilities, it is found that in five cases bacteria were recovered from the anal areas only, in four cases different species were isolated from anal areas and the corresponding meconium specimens, and in only four cases were the species from the two sources identical. Therefore, it would appear that only the last four cases should be eliminated on the ground of exterior contamination. In addition, there were six cases in which no skin cultures were made. One was sterile, one had hemolytic streptococci in the meconium as demonstrated by direct plating, and the other four were positive for bacteria by enriching methods. If the four cases of duplication and the four positive cases with no skin cultures be eliminated from the series, there remain fifty-six specimens of meconium from the series, in twenty of which bacteria were demonstrated

by enrichment methods. These results indicate the presence of only a few bacterial cells, except possibly the cases from which anaerobes were isolated, in the meconium.

In this series the percentage of positive results with solid media was only 6.3 per cent, which is much lower than the 23 per cent reported by Hymanson and Hertz,12 the 38 per cent by Burrage,14 and the 30 per cent by Hall and O'Toole.15 Enrichment results gave 35.7 per cent, a figure which is not significantly different from the 38 per cent obtained by Hall and O'Toole with both solid and enrichment media. It is possible that some of the discrepancies may be explained by the failure of Hymanson and Hertz to cleanse the skin of the anal area before the specimen was collected, and that Burrage, Hall and O'Toole limited their studies to first passage specimens. Hall and O'Toole reported specimens microscopically positive which were collected thirteen, twenty-six, and seventeen hours, respectively, after birth which findings led Hall (personal communication) to believe that postnatal bacterial invasion accounted for many of the positive results in the study of first passage meconium specimens. The present investigation was designed to cover these points and to get the specimens within a short period after delivery under aseptic precautions, and it would seem that the positive cases reported furnish reliable evidence that bacteria are present in the meconium at birth in a small percentage of cases. Thus the essential point in this investigation is not that the solid media results are so greatly different or that the enrichment results approximate the figures given previously, but that the meconium is not always sterile at birth.

To explain the presence of bacteria in the meconium of newborn infants in numbers to be demonstrated by plating or enrichment media, if contamination can be ruled out, three routes of infection may be considered. First, it is possible that bacteria invade the meconium during passage of the fetus through the birth canal, but the natural process of delivery prevents any serious investigation. Second, the bacteria may have been deposited in the intestine from the blood stream. In this study no attempt was made to run control tests on the blood of the mother and child. Third and most plausible, the amniotic fluid may have been infected by the organisms of the vaginal flora. Since the fetus is surrounded by amniotic fluid, which enters the intestinal tract, as evidenced by the presence of lanugo hair, epidermal cells, and vernix caseosa in the meconium,17 it would not be unreasonable to expect bacterial invasion of the meconium if the fluid became infected. Therefore, a relation should exist between the time of rupture of the fetal membranes and birth with the appearance of bacteria in the meconium; that is, the longer the time between fetal membrane rupture and delivery, the greater should be the chance of finding bacteria in the intestinal tract. A similar relation of time between rupture and inflammation of the fetal membranes and congenital pneumonia in stillborn and newborn

infants dying in the first three days was pointed out by Johnson and Meyer. 15 Hall and O'Toole, 15 however, could not show that time elapsing from rupture of the fetal membranes to birth influenced the presence of bacteria in fifty first passage meconium specimens. Similarly, in the present study little or no relation could be established between the time from fetal membrane rupture to delivery, inflammation in the membranes, and the presence of bacteria in the meconium of fifty of the sixty-four cases studied.

#### SUMMARY

In three of twenty-nine specimens of meconium collected within thirty minutes after delivery, bacteria were demonstrated by plating methods. These three positive cases indicate that prenatal bacterial invasion of the intestinal tract does occur in a small percentage of cases.

Some of the positive results obtained by enrichment might be invalidated by the failure to sterilize thoroughly the skin surrounding the anus, but a large number with corresponding sterile skin cultures, or skin cultures showing other bacterial species than in the meconium, indicated that a few organisms were present in the meconium at birth in about 36 per cent of this series of sixty-four specimens.

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# THE BACTERIAL FLORA OF THE INTESTINAL CONTENTS OF TWENTY-SEVEN STILLBORN INFANTS

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IT WAS shown in a preceding study of newborn infants that bacteria could be demonstrated by plating methods in three of twenty-nine specimens of meconium collected within thirty minutes after delivery. These findings indicated that bacteria were present in the intestinal tracts of infants at birth in a small percentage of cases. In order to study further the occurrence of bacteria in the intestinal tract at birth, segments of the intestines of twenty-seven stillborn\* babies were examined.

Despite the large amount of work recorded on the sterility of the meconium at birth and the bacterial invasion of normal living infants, only two references dealing directly with intestinal examinations of still-born material were found in the available literature. Both Escherich,<sup>2</sup> who examined three stillborn infants, and Popoff,<sup>2</sup> who killed newborn kittens and puppies, were unable to demonstrate bacteria in any of these and concluded that the fetal meconium was sterile at birth.

#### METHODS OF COLLECTION AND EXAMINATION

In the first fifteen cases only one segment was taken from the intestinal tract. This was from the ascending colon as close as possible to the cecum, and was selected because it was thought to be least exposed to either oral or anal bacterial invasion. Therefore, if bacteria were found, it would seem indisputable evidence that bacteria were present in the intestinal tract at birth. In the remaining twelve cases segments were taken from the descending colon, ascending colon, ileum, and duodenum. The segments were tied off, cut, and placed in sterile Petri dishes, and in the first fifteen cases they were dipped momentarily in boiling water. Those from the other twelve were seared with a hot spatula. tions were opened with instruments that had been boiled or flamed. Smears of the contents were stained by Gram's method and were negative except in one case where large gram-positive rods were observed. The contents were also streaked across cosin methylene blue and blood agar plates and were placed in freshly boiled and cooled deep brain medium.

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\*No distinction is made between the terms "stillborn" and "deadborn."

#### RESULTS

The fifteen infants from whom only one section of the intestine was taken are recorded in Table I in the order of the time elapsing between death and autopsy.

Table I shows there is apparently little relationship between the time of delivery and autopsy and the presence of bacteria in the intestines

TABLE I

BACTERIAL FLORA OF THE INTESTINAL CONTENTS AT THE ASCENDING COLON
OF 15 STILLBORN INFANTS

	1		RESULTS		
No.	Hours*	SECTION	PLATES	ENRICHMENT	
1	3	Ascending colon	Sterile	Sterile	
2	14	Ascending colon	Sterile	Sterile	
3	181	Ascending colon	Sterile	Sterile	
4	27	Ascending colon	Sterile	Sterile	
5	30	Ascending colon	Sterile	Sterile	
6	30	Ascending colon	Sterile	Sterile	
7	57	Ascending colon	Sterile	Sterile	
8	63	Ascending colon	Sterile	Sterile	
9	66	Ascending colon	Sterile	Sterile	
10	66	Ascending colon	Sterile	Sterile	
11	72	Ascending colon	Sterile	M. aureus	
12	73	Ascending colon	Sterile	Sterile	
13	109	Ascending colon	Sterile	M. epidermidis	
14	9	Ascending colon	Sterile	Sterile	
15	9	Ascending colon	Sterile	Sterile	

<sup>\*</sup>Time in hours between delivery and autopsy.

of stillborn infants. In only two of the fifteen cases were bacteria demonstrated, and in both of these only after enrichment. These cases are discussed in detail as follows:

Case 11.—No clinical history was available for this premature infant, who weighed about 5 pounds. Autopsy revealed extensive subarachnoidal hemorrhage. Other sites of hemorrhage were in the pleurae, epicardium, scalp, tentorium cerebelli, and falx cerebri. The heart's blood was sterile. M. aurcus was isolated by enrichment from the ascending colon. Time of the rupture of the fetal membranes and the condition of the membranes and placenta were unknown.

CASE 13.—This premature infant of about six months' gestation was apparently dead from the nephritic toxemia of the mother. Autopsy showed slight maceration, petechial hemorrhages in the thymus, parietal pericardium, epicardium, scalp, and epicranium, and slight congestion of the cerebrum. The membranes ruptured eighteen and one-half hours before delivery and were acutely inflamed. The heart's blood was sterile. M. epidermidis was isolated from the ascending colon by enrichment. The mother made an uneventful recovery.

The significance of the positive enrichment cultures will be considered in the discussion.

The bacteriologic study of the sections taken from various portions of the intestinal tract of twelve stillborn infants is given in Table II.

In contrast to the first series, the data presented in Table II show that the intestinal contents of only one of twelve stillborns to be sterile in

TABLE II

BACTERIAL FLORA OF THE CONTENTS OF VARIOUS PORTIONS OF THE INTESTINAL
TRACT OF STILLBORN INFANTS

				1 Comming	DESCENDING
NO.	TIME	DUODENUM	ILEUM	ASCENDING	· ·
	HOURS*			COLOX	COLOX
16	14	Sterile	Sterile	Sterile	M. epidermidis
	1	}		1	Str. fecalis
17	163	B. welchut	B. welchut	B. welchut	B. welchirt
18	22	Sterile	Sterile	Sterile	M. citreus
					Str. nonhemolyticus II
19	23	Sterile	Sterile	Sterile	Sterile
20	24	Sterile	Sterile	Sterile	B. alkaligenes;
					M. flarust
	}		Į		Str. ignarus;
21	24	B. alkaligenest	Sterile	Sterile	M. citreus
					B, coli
22	24	Sterile	Sterile	M. aurantiacus	B. coli
23	281	B. tertius	Sterile	Sterile	Sterile
24	30	Sterile	Sterile	Sterile	B. colı
					Sarcina lutea
25	30	Sterile	M. luteus;	M. luteus;	M. luteus;
26	50	C. hofmanni;	Sterile	Sterile	Sterile
27	53	Sterile	Sterile	Sterile	M. varians‡

<sup>\*</sup>Time in hours between delivery and autopsy.

sections taken from the duodenum, ileum, ascending colon, and descending colon. Bacteria were isolated by direct plating and enrichment methods in the other eleven cases These cases are reported as follows:

CASE 16.—This was a full term infant, weighing about 9 pounds, anatomically normal. The heart's blood was sterile. M. epidermidis and Str. fecalis were isolated by enrichment from the descending colon.

The mother had a massive hemorrhage from a duodenal ulcer before she was brought to the hospital on the evening before delivery. Fetal movements could not be discerned at the time of entrance. Death of the baby was believed to be due to the anemia of the placenta which resulted from the hemorrhage; the placenta and membranes were free from inflammation

Case 17.—The body was that of a full term child who weighed about 8 pounds. The delivery was a breech presentation, and apparently the head was retained in the cervix until death occurred. The placenta, the membranes, and the cord were acutely inflamed. Autopsy showed atelectasis, slight bilateral tentorial tears with no hemorrhage, and aspiration of amniotic fluid. Large gram positive rods were observed microscopically in the duodenum, the ileum, the ascending colon and the descending colon. These were isolated and identified as B. welchii. Since the child was born in this hospital and remained most of the sixteen and three-fourth hours from birth to autopsy in the ice box, it would seem that the presence of organisms in sufficient number to be demonstrated microscopically would be clear cut evidence that the bacteria invaded and multiplied in the meconium before birth.

CASE 18—This full term, 8 pound infant was delivered by version and extraction after a shoulder presentation was determined. The cord was not pulsating before the patient was taken to the delivery room. The placenta was normal; no information was available about the rupture of the membranes. Autopsy revealed a broken neck

<sup>†</sup>Observed microscopically in contents.

Isolated by direct plating.

and atelectasis. The heart's blood was sterile. The inoculated plates were negative, but M. citrcus and Str. nonhemolyticus II were isolated by enrichment from the descending colon.

Case 20.—The clinical history furnished no definite reason for the death of this 6½-pound full-term infant. The doctor who delivered this case in an outside institution reported a velamentous insertion of the cord with rupture of the membranes adjacent to the site of insertion, but there was no record of hemorrhage. The gross pathology was limited to atelectasis. B. alkaligenes, M. flavus, and Str. ignavus were isolated by both plating and enrichment from the descending colon.

Case 21.—This was a premature infant of about the seventh lunar month of gestation, weighing about 3 pounds. It was brought in from another hospital, and no information was secured about the clinical history. Autopsy showed pneumothorax. B. alkaligencs was isolated by both plating and enrichment methods from the duodenum; M. citreus and B. coli were isolated by enrichment from the descending colon.

CASE 22.—This was a full-term infant who was delivered in another hospital. The mother's labor was prolonged. Forceps were applied unsuccessfully and with heavy laceration which apparently caused the death of the baby. The body had already been opened. No heart's blood was taken, but M. aurantiacus was isolated from the ascending colon by enrichment, and B. coli was recovered from the descending colon after enriching of the contents.

Case 23.—This infant was about one month premature, and weighed about 5 pounds. The heart was beating at birth, but no respirations were made. The delivery was a footling presentation, and great difficulty was encountered in removing the head. Membranes ruptured about one and a quarter hours before delivery; the placenta was normal. The heart's blood was sterile. Tentorial tears with resultant hemorrhage were found at autopsy. B. tertius was recovered by enrichment from the duodenum. All other cultures were sterile.

Case 24.—The body was that of a full-term infant weighing 8½ pounds. It was born in an outside institution, and no clinical history was available. Autopsy showed tentorial tears with hemorrhage. The heart's blood was sterile. Sarcina lutea and B. coli were isolated by enrichment from the descending colon.

Case 25.—This was a full-term infant whose heart was beating up to twelve hours before delivery but was not beating at birth. There was no apparent clinical cause for death. Autopsy showed moderate congestion of the lungs and some "congenital pneumonia." The heart's blood was sterile. The membranes were moderately inflamed, having ruptured thirty hours before delivery. M. lutcus was isolated directly by plating methods from the ileum, the ascending colon and the descending colon.

Case 26.—This full-term infant was delivered after a breech presentation. The heart was beating, but the infant made no attempt to breathe. Resuscitation was abandoned after forty-five minutes. Autopsy showed fetal atelectasis and tentorial tears. The membranes ruptured two hours before delivery; neither placenta, membranes, nor cord was inflamed. The heart's blood was sterile. From the white mucoid material of the jejunum, which was microscopically negative, C. hofmanni was isolated by direct plating. The other sections were sterile.

Case 27.—This infant was slightly premature and was delivered dead after a breech presentation. Autopsy showed fetal atelectasis and a patent intraventricular

septum. The heart's blood was sterile. Three colonies of M. varians were found at the beginning of the streak on blood agar, and this species was also isolated by enrichment. All positive cultures were obtained from the descending colon.

If the study is analyzed in respect to the intestinal segments studied rather than according to the case, it is noted that four of the twelve duodenal specimens yielded bacteria, and in three of the four cases organisms were demonstrated by plating methods or microscopically. Only two ileal segments were positive but one showed bacterial cells when examined microscopically. Bacteria were demonstrated three times by plating and enrichment in the ascending colon sections and once microscopically. Nine of the twelve descending colon segments showed bacteria to be present by plating or enrichment methods, and one, microscopically. This might indicate a more frequent per anum bacterial invasion of the intestine than per os.

Sixteen species were isolated from the intestinal contents of the twenty-seven stillborn infants. Their frequence is given as follows: B. coli, B. alkaligenes, and M. citreus, three times; M. epidermidis, two times; and M. flavus, M. luteus, M. varians, M. aureus, M. aurantiacus, Str. ignavus, Str. fecalis, Str. nonhemolyticus II, C. hofmanni, B. welchii, B. tertius, and Sarcina lutea, once each.

#### DISCUSSION

Proof for prenatal bacterial invasion of the intestinal tract in stillborn as with newborn infants depends entirely upon microscopic and cultural examination of the intestinal contents. The presence of organisms in the intestinal contents of a stillborn child as demonstrated by the microscope soon after birth would seem to furnish absolute proof that bacteria may be present at or before birth. The observation of gram-positive rods similar to B. welchii, which was subsequently isolated, in Case 17, is offered as the most suggestive evidence in this series. Next in value to microscopic proof is the culturing of organisms directly on solid media so that the position and number of the resultant colonies cannot be mistaken for contamination. This condition occurred in Cases 20, 21, 25, and 26. Positive enrichment cultures are least valuable because growth in liquid media may result from either too few organisms to be demonstrated by plating methods or from exterior contamination. Although there was no skin sterilizing factor in this study, the surfaces of the segments had to be cleansed. This was accomplished by either dipping momentarily into boiling water or searing with a spatula. The segments were opened with either freshly boiled or flamed scissors and forceps. Despite these precautions the isolation of such organisms as Sarcina lutea would lead one to doubt the validity of positive enrichment results in all cases. This leaves the obvious conclusion that reliable data are best obtained with solid media and positive microscopic evidence.

Three possible methods for prenatal invasion of the intestinal tracts of stillborn infants are to be considered: (1) neonatal septicemia, (2) infection of the amniotic fluid, and (3) during passage of the fetus through the birth canal.

A possible relation exists between the septicemias of the stillborn and the organisms found in the intestinal tracts of these cases. Some cases of neonatal septicemias have been described in detail by Slemons, Del.ee, and Serbin. In the present series only two of twenty-one cases gave positive blood cultures at autopsy, and the organisms isolated, M. tetragenus and Bact. pyocyaneum. respectively, were not recovered from the intestine in any case studied. Therefore, it may be said that there was no correlation between the organisms isolated from the heart's blood and those isolated from the intestinal tract in this group of stillborn infants.

The early rupture of the fetal membranes with subsequent infection of the amniotic fluid by the vaginal organisms and invasion of the intestinal tract of the fetus either per os or per anum or both offers the most plausible method of infection. The somewhat analogous rôle between early rupture of the fetal membranes and congenital pneumonias in the newborn and stillborn was pointed out by Johnson and Meyer.7 However, Hall and O'Toole's could not establish any relation between the time clapsing between the rupture of the fetal membranes and the presence of bacteria in the first passage of meconium. In the preceding study of a series of sixty-four specimens of meconium from newborn infants collected within four hours after delivery,1 this relationship could not be determined. It seemed important, nevertheless, to compare the stillborn with the normal newborn in this respect. It was difficult to secure accurate information about the rupture of the fetal membranes; the available data, however, are listed in order of increasing time from rupture to delivery, and the histologic examination of the placentas in these and other cases is also included in Table III.

Too few cases are included in Table III to establish any definite relation between the time elapsing between rupture of the fetal membranes and delivery, the condition of the membranes, and bacteria in the intestinal contents of stillborn infants. It does seem significant, however, that in four of the five cases showing moderate to acute inflammation of the fetal membranes, bacteria were isolated from the intestinal contents. On the other hand, *C. hofmanni* was isolated directly in large numbers from Case 5 in which the membranes ruptured allegedly forty-five minutes before delivery and the fetal membranes showed no sign of inflammation, and in Case 13 the fetal membranes were acutely inflamed, but no bacteria were isolated from the intestinal contents.

This problem is confused by the inability to collect accurate information about the rupture of the membranes because so-called "high" ruptures may pass unnoticed but permit invasion of the amniotic fluid by

TABLE III

RELATION BETWEEN THE TIME OF RUPTURE OF THE FETAL MEMBRANES TO DELIVERY,
INFLAMMATION OF THE MEMBRANES, AND THE PRESENCE OF BACTERIA
IN THE INTESTINAL CONTENTS OF STILLBORN INFANTS

NO.	TIME IN HOURS*	CONDITION OF FETAL MEMBRANES	BACTERIAL FLORA OF THE INTESTINAL CONTENT
1	At birth	Normal	Sterile
2	At birth	Normal	Sterile
3	At birth	Normal	Sterile
4	At birth	Normal	Sterile
<u>4</u> 5	0:45	Normal	C. hofmannit
6	4:45	Normal	Sterile
7	14:30	Normal	Sterile
8	15:45	Normal	Sterile
9	17:00	Acute inflammation	B. welchii‡
10	18:45	Acute inflammation	M. epidermidis
11	30:00	Moderate inflammation	M. luteust
12	9	Acute inflammation	M. aureus
13	9	Acute inflammation	Sterile
14	9	Normal	Sterile
15	9	Normal	Sterile
16	9	Normal	Sterile
17	9	Normal	M. citreus
_,			Str. nonhemolyticus II

<sup>\*</sup>Time in hours from rupture to delivery.

the vaginal flora. After membrane rupture some time must elapse before bacteria can multiply in the amniotic fluid, and then the fetus may or may not swallow the infected fluid. The same possibility exists for the invasion by bacteria per anum. The fetus may be delivered before inflammation of the membranes occurs and still have bacteria in the intestinal tract. Finally, the hygiene of the individual mother frequently determines the number and type of organisms in the vaginal tract<sup>9</sup>; that is, the flora ranges from a homogenous but scanty flora of gram-positive rods, Doederlein's bacillus or L. acidophilus, of with a highly acid secretion (Grade I) to a mixed flora with a more alkaline secretion (Grade III). Thus it is probable that the type of vaginal flora determines the amount of infection of the amniotic fluid and in turn the organism isolated from the intestine of the newborn and the stillborn infant.

The remaining possible route of prenatal infection of the intestinal tract is during the passage of the fetus through the birth canal. As in the newborn series this mode of invasion could not be studied seriously.

#### SUMMARY

The presence of *B. welchii* microscopically and culturally in the duodenum, the ileum, the ascending colon and the descending colon of a stillborn infant is considered as reliable evidence that bacteria may invade the intestinal tract of the infant before or during birth. Additional evidence of slightly less value was obtained by finding numerous

<sup>†</sup>Isolated by plating.

<sup>#</sup>Observed microscopically.

colonies along the streaks on plates inoculated from the intestinal contents of four stillborn infants. The results obtained by enrichment were regarded as of doubtful significance because of the possibility of accidental contamination, except in the one case where B. welchii was isolated after being observed microscopically.

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## ACTIVE ARTIFICIAL IMMUNIZATION IN DIPHTHERIA

THE RELATIVE EFFECTIVENESS OF VARIOUS ANTIGENS AND THE DURATION OF IMMUNITY

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ALTHOUGH the value of diphtheria immunization is unquestioned, there is still some uncertainty about the best method of producing it; i.e., the method which will result regularly in the maximum percentage of immune subjects with a minimum of injections and unpleasant reactions. Certainly, effectiveness and simplification are the two primary requisites for any method of immunization advised on a large scale. The high incidence of susceptibility in children, especially those in the preschool age, has led to the general acceptance of the view that preliminary Schick tests in children should be omitted and that every child should be immunized. Another advance in simplification of the general procedure will be made when a method of immunization can be shown to result regularly in such a high percentage of immunes that subsequent Schick testing may be safely omitted.

This report summarizes the results of immunization against diphtheria in more than 500 young adult student nurses during an eighteen-year period, with the use of several types of antigens and with a variance in the number and spacing of the injections. A number of subjects immunized from six to sixteen years previously were retested to determine the duration of the immunity.

Methods.—All student nurses of the Washington University Nurses' Training School were given Schick tests in groups of 15 to 50 early in their probation period during the years 1918-1935. Those with positive tests were immunized and were retested from four to six months later. This interval of several months before a retest seems important since in several instances Schick tests which were negative four to six weeks after immunization had again become positive three to four months later. Any who remained Schick-positive were given a second immunization identical with the first, usually from six to ten months after the initial injections. Previous to 1925 the Schick test toxin and immunizing antigens were obtained from the New York City Board of Health, and since then all material has been furnished by Eli Lilly and Company. Controls of the identical toxin preparation used for the Schick test heated for five minutes to 75° C. were always included, and readings of the tests and controls were made on the fourth day. All tests, readings, and im-

munizations were done by the author to guarantee uniformity in interpretation and procedure. Some pupils who left training before immunization was finished are omitted from the tabulations, only those being included upon whom complete observations were made.

Results.—Susceptibility: Of 1,054 nurses tested, 664, or 63 per cent, gave positive Schick tests. A large proportion of these girls came from rural or suburban communities and a rather high percentage of susceptibility seems to be the rule in persons not reared in larger cities where diphtheria is endemic.

TABLE I
RESULTS OF DIPTHERIA IMMUNIZATION BY VARIOUS PROCEDURES

ANTIGEN USED	DOSES	INTERVAL	NUMBER VACCINATED	PER CENT NEGATIVE
I. T.A.T. (3L+)	3	1 wk, + 1 wk,	62	79.0
T.A.T. (2nd set)	3	1 wk. + 1 wk.	8	38.0
2. T.A.T. (0.1L+)	3	1 wk. + 1 wk.	274	59.3
T.A.T. (2nd set)	3	1 wk. + 1 wk.	96	92.6
T.A.T. (3rd set)	3	1 wk. + 1 wk.	5	100.0
3. Toxoid	2	3 wk.	53	75.5
Toxoid (2nd set)	2	3 wk.	13	92.4
Toxoid (3rd set)	2	3 wk.	1	100.0
4. Toxoid	2	õ wk.	46	78.2
Toxoid (2nd set)	2	5 wk.	10	100.0
5. Toxoid	3	3 wk. + 2 wk.	37	100.0
6. A.P. Toxoid	1	~	64	80.0
A.P. Toxoid (2nd set)	1	4.5 mo.	13	100.0

Immunization: The results of the immunizations with the various antigens have been summarized in Table I. In the two groups (1 and 2) with toxin-antitoxin (T.A.T.), it will be noted that a single series of three injections at weekly intervals did not regularly produce as high a percentage of immunes as might be expected. This was especially true of the 0.1L+ antigen which produced about 59 per cent of immunes. A second series of three injections resulted in the immunization of a very large proportion of the remainder, and the small number not immunized by the preceding injections became Schick-negative after a third set. The results with two doses of toxoid (Groups 3 and 4, Table 1) given at an interval of three weeks or five weeks were quite similar to those from toxin-antitoxin. When three doses of toxoid (Group 5, Table I) were given at intervals of two and three weeks, the results were much better. A single dose of alum-precipitated toxoid resulted in only 80 per cent immunes, but a second dose immunized all the remainder. Although a few required a third set of injections with toxin-antitoxin and with toxoid, all became Schick-negative eventually.

In the immunization of infants and young children, it has been our experience, as well as that of others, that a rather high proportion of those inoculated with two doses of toxoid or a single dose of alumprecipitated toxoid develop negative Schick tests. There is a very definite impression, however, among certain health officers in rural communities that the response to diphtheria immunization is less satisfactory in rural children than that reported in cities. It may be that the relatively lower percentage of immunes obtained among the young adults here reported after their first series of injections is related to the fact that a large proportion of them were reared in suburban communities or that adults are more difficult to immunize with the same doses used in children. At any rate, the fact that, as a group, these nurses responded only moderately well to the initial vaccination gave a somewhat better opportunity to observe the relative effectiveness of the various procedures used.

Certain features of the results may be summarized briefly. Toxoid and especially alum-precipitated toxoid were relatively more effective than toxin-antitoxin. Two doses of toxoid or a single injection of alum toxoid immunized only 75 to 80 per cent. By far the best results were obtained by two doses of alum-precipitated toxoid, the second after a considerable interval, and by three doses of plain toxoid separated by intervals of several weeks. This tends to confirm the well-known experimental observations that the immunity following the first or "primary" response to the diphtheria antigen is slow, feeble and transient, but the "secondary" response following a later antigen stimulus results in rapid, pronounced and persistent antitoxin formation. would appear, therefore, that those who become immune following a single injection or series of injections have already responded previously to the diphtheria antigenic stimulus such as occurs in the development of "natural immunity," and develop the permanent immunity characteristic of a "secondary" stimulus. On the other hand, those who have not reacted previously to the diphtheria antigen and consequently do not become immune following a single injection or series of injections will require a second immunization. It was hoped that alum toxoid, being insoluble and, therefore, slowly absorbed, would serve as both the primary and secondary stimuli and that a single antigenic injection would be adequate. The results in the series reported here, however, do not confirm this, since 20 per cent of those receiving a single dose remained Schick-positive.

The results obtained by the several methods used indicate that the maximum percentage will be immunized by two doses of alum toxoid with an interval of one to several months between them. While a considerable number may be immunized by a single injection, the percentage remaining Schick-positive is sufficient to warrant the advisability of giving a second later dose whenever possible. The larger number of

injections of toxin-antitoxin and plain toxoid make them less desirable for routine use, although the latter seems quite effective when given in three doses at intervals of about three weeks.

Reactions following toxoid injections are rare in infants and young children although often a somewhat tender nodule persists for some days after alum-precipitated toxoid. The occasional occurrence of moderately severe local pain and swelling accompanied by a febrile general reaction in older children and more frequently in adults has tended to limit the use of toxoid and alum toxoid. During the past six years several hundred young adults (nurses and medical students) have been given toxoid and alum toxoid. Most of them have had a slight local reaction only, while a few have had headache, mild fever, and malaise for the day following. Alum-precipitated toxoid seemed somewhat more likely to produce such an effect than plain toxoid. Rarely a very severe local reaction with general febrile toxic symptoms has occurred and persisted for several days.

In general, such reactions have been only slightly more severe than those following toxin-antitoxin and there has been no suggestion of discontinuing the use of toxoid because of them. It must be emphasized, however, that the foregoing applies only to the products of one manufacturer used routinely. In the few instances in which two other commercial toxoid antigens were tried, the number and the severity of the reactions were so great that they were considered unsuitable for use in adults.

Clinical Results.—All student nurses of the group tested spent from four to six weeks on duty in the contagious wards of the St. Louis Children's Hospital where they attended patients with clinical diphtheria as part of their training. During the three years immediately preceding the adoption of immunization in 1918, seventy student nurses were on duty in the contagious wards and twenty of them developed clinical diphtheria. Since 1918 only two cases of diphtheria have occurred among almost 1,000 students, both in known nonimmunes, accidentally exposed to the disease before immunization. This contrast in incidence before and after immunization is striking proof of the clinical effectiveness of the procedure in persons intimately exposed.

Duration of Immunity After Active Artificial Immunization.—The immunity which develops after diphtheria vaccination has generally been assumed to be lasting, although it is the general belief that in many instances the artificial immunity produced by injections merely protects the child over a certain limited period of susceptibility to diphtheria, and that during this time many develop an additional "natural immunity" which is solid and permanent. This belief is fostered by the frequent observation that even without artificial immunization there is a considerable tendency for older children and adults to have negative

Schick tests. That this tendency is apparently not constant, however, is shown by the fact that, in the adult nurses reported in this paper, 63 per cent were still susceptible. While in occasional instances diphtheria has occurred in vaccinated children, it has been extremely rare in those known to have been Schick-negative after vaccination. The published observations, however, on the duration of immunity based on Schick tests done some years after vaccination have been few because of the difficulty of collecting groups of immunized persons some years afterward. Such as I have been able to find are given in Table II. The first two show the results after toxin-antitoxin while the others report results with Ramon's anatoxin. The largest series, that of the Mosers (often mistakenly attributed to Ramon in the literature), gives somewhat misleading percentages, since no previous Schick tests had been made and many children may have been immune even before the anatoxin injections. In general, the results reported, however, indicate that the immunity

TABLE II

DURATION OF IMMUNITY AFTER ACTIVE IMMUNIZATION

OBSERVER		INTERVAL AFTER IMMUNIZA- TION— YEARS	NUMBER TESTED	PER CENT SCHICK- POSITIVE
Schroeder	T.A.T.	5	28	10.7
Parish and Okell	T.A.T.	1 to 4	440	5.0
Moser, M., and Moser, G.	Ana.	2	498	5.0
• •		3	162	4.3
		4	250	3.6
Cerruti	Ana.	21/2	29	17.2
Calisti	Ana.	1	54 (adı	ilts?) 0.0
Bosco	Ana.	4	10	40.0
Ronchi	Ana.	5	27	14.8

persists in a large proportion of those vaccinated. Many of those found to have positive Schick tests later were observed to become reimmunized quickly after another vaccination.

In the groups of young adult nurses considered in this report, 102 were retested six to sixteen years after immunization by toxin-antitoxin and subsequent negative Schick tests. Of these, 12 had been done fourteen to sixteen years previously, and three of these, all after sixteen years, again gave positive Schick tests, one of them only weakly positive. Ninety who had received the injections six to twelve years previously included only two with positive tests, one of these (after nine years) being strongly positive and the other (after eight years) being only faintly positive. The fact that more than 95 per cent of this group of 102 were immune from six to sixteen years after vaccination is striking proof of the degree of effectiveness and persistence of the protection afforded by active artificial diphtheria immunization.

#### SUMMARY

In more than 1,000 young adult student nurses, 63 per cent were found susceptible to diphtheria by the Schick test.

Groups were immunized by toxin-antitoxin, toxoid, and alum-precipitated toxoid over a period of eighteen years. Of the methods tried, the most effective procedures were found to be (1) two injections of alum toxoid with an interval of several months between or (2) three injections of plain toxoid with intervals of several weeks between the doses.

As a result of immunization, the clinical incidence of diphtheria among these nurses has been reduced from 28.6 per cent to 0.2 per cent.

In a group of 102 nurses, immunized by toxin-antitoxin and retested six to sixteen years later, more than 95 per cent were still immune.

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# MECHANICAL LESIONS OF THE APPENDIX IN CHILDREN AS A BASIS FOR APPENDICITIS

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THIS is an investigation based on the study of 127 consecutive cases of mechanical lesions affecting the appendix in children exhibiting symptoms not generally attributed to a disturbance of this organ, but clearly distinguishable by clinical and laboratory investigation. These findings were confirmed in all cases by careful study of the gross anatomical changes at operation, as well as by microscopic examination. In these lesions was found a basis for an explanation of a large number of cases of appendicitis in both childhood and adult life generally considered as acute primary forms. A diagnosis of mechanical lesions of the appendix was possible at such an early stage that by surgical removal of the causative factor the mortality rate was kept at a minimum. In this series it was zero.

It is also proposed to show that by early surgical intervention, not only is mortality reduced, but the nutritional development of the children, by its return to the normal, produces ideal weight and development.

This work on mechanical conditions in and around the appendix was suggested by the failure of some cases of bad posture in children to improve when abdominal supports were applied, or if they did improve they failed to maintain their improvement. In a certain number there were associated mild attacks of abdominal pain; a diagnosis of chronic appendicitis was made; and appendectomy was performed. At operation distinct mechanical lesions in and around the appendix were found and removed together with the appendix. The symptomatic relief and the nutritional improvement were so marked and rapid that they led to a very careful survey of similar cases; these after appendectomy had equally good results. This work clearly demonstrates the value of accurate laboratory work, the importance of very careful and detailed histories, and a diagnosis largely by exclusion.

Mechanical conditions involving the appendix have been described by numerous authors under the headings of "chronic appendicitis," and "appendical syndrome." The subject, "chronic appendicitis," has been a controversial one in surgical circles for years. Myers<sup>1</sup> quotes Watkins as reviewing 662 papers up to 1932 and reviews the literature to September, 1934. In his summary he states: "The more

recent literature, especially that of the last five years, on chronic appendicitis indicates a growing opinion that there is such a malady, that it is more prevalent, more dangerous, and more frequently overlooked than has been previously taught. Indications are that failures of the past have been largely due to a lack of diagnostic thoroughness. Certain medical centers have published statistics showing from 60 to 90 per cent of the patients who had operations for chronic appendicitis were completely relieved by appendectomy alone. Muller recently (1932) has said that a campaign of instruction of the public regarding appendicitis is more important than a campaign against cancer. It seems fair to say that such a campaign should be directed to the laity regarding acute appendicitis, but a like campaign is needed for the profession regarding chronic appendicitis.'

Freed<sup>2</sup> states, "In the United States and Canada twenty-five thousand die yearly from acute appendicitis, that is one death every twenty-five minutes, or seventy deaths every day, Sundays and holidays included, and the mortality is on the increase." In childhood there is an average mortality of about 14.5 per cent.

Farr<sup>3</sup> states, "I also believe that there is such an entity as chronic appendicitis and that it applies to children fully as often as to adults." Tenny<sup>4</sup> is convinced of the importance of a mechanical obstructive condition in and around the appendix as a producer of appendicitis, and he emphasizes reflex constipation and pylorospasm. Wilkie, <sup>5, 6</sup> one of the first to describe acute obstructive appendicitis, lays emphasis on constriction of the appendical lumen, with associated fecal concretions, and describes both an acute and a chronic form.

In making a diagnosis of mechanical conditions in and around the appendix, it is first necessary to know the normal anatomy. The appendix hangs down freely from the cecum and has a uniform and patulous lumen, and a terminal and limited arterial blood supply. Any kinking, twisting or constriction of the wall of the appendix, whether produced by Lane's bands. Jackson's membrane, short mesentery, or constriction of the lumen due to contracting fibrous tissue from a previous inflammatory reaction, will cause fecal retention, and this in turn will produce chronic irritation of the appendix. Through the sympathetic and vagus nerves, there is an intercommunication with the stomach, often producing pylorospasm with nausea or vomiting, or with the colon, producing spastic constipation.

When the lumen of the appendix is constricted, fecal material may be forced in from the cecum. But since the weaker contraction of the appendical wall is not able to evacuate completely the contents, a portion remains, and its moisture is absorbed through the appendical wall and produces a beginning inspissation which may lead to concretion. If this change is not severe enough to obstruct the lumen completely,

there are chronic symptoms, such as pain, spastic constipation, "bilious attacks," vomiting, etc. If the concretion completely obstructs the lumen, more severe changes may follow, often ending in gangrene. These cases produce, according to Wilkie, 5, 6 90 per cent of the mortality of acute appendicitis. On the other hand, a constriction of the blood supply from a twist, short mesentery, membrane, or bands, causes edema of the wall and predisposes to an inflammatory process.

A typical history is that of a child who has had short attacks of recurrent abdominal pain for a considerable period, either daily or at longer intervals. The pain varies from a dull ache, a burning sensation, or sense of fullness to one of a sharp stabbing character. attacks may be very fleeting but they have a marked tendency to recur, and at times there is associated nausea or actual vomiting. recurrence of attacks, in spite of a well-regulated simple diet and good hygiene, is of great significance. Children often stop in their play, turn a little white, have a slight generalized abdominal pain, over in an instant. These cases are commonly diagnosed as indigestion. is very likely to come on during or from one-half to two hours after a meal, or pains may have no relation to food intake. Pain frequently is increased by exercise, its location is umbilical or epigastrical at first, but later may become localized in the right iliac fossa. A bowel movement, passage of gas, or vomiting usually gives prompt relief. There are associated poor color, poor muscle tone, poor nutrition, and poor posture. Abdominal supports will often relieve the symptoms for a time, but there is frequently a recurrence. This failure to produce a permanent cure with abdominal supports is very suggestive. There is poor appetite, and constipation is the rule. The temperature, pulse, respiration, and blood count at this time are normal. A careful abdominal examination at the time of the attack will reveal in most cases slight deep right iliac tenderness with but little if any muscular rigidity. If a review of the family history reveals appendicitis in the near relatives, it is very suggestive, as heredity seems to play an important part; in this series the rate was 63 per cent. The physician should inquire as to any pylorospasm in infancy and any causeless attack of vomiting or cyclic vomiting, as in our 127 cases 66 per cent had vomiting and 6 per cent cyclic vomiting.

Later pain may move over to the lower right quadrant. A white blood count with careful study of the neutrophiles, including a nuclear shift, then shows slight irritative changes but not much elevation of the total count. As the case becomes more acute, there may be a slight temperature elevation during the attacks. At operation bands, adhesions, Jackson's membrane, a short mesentery, or stricture of the appendix with fecal concretions is found. The appendical lumen usually shows cystic dilatation and some atrophy of the mucous mem-

brane with a possible old fibrosis of the walls from a previously healed acute attack. If operation is performed very early in the course of the infection, no appendical lesion may be found.

Another frequent type is that found in a child who has been in apparently good health, but usually whose nutrition is poor, as shown by a searching history. He goes to bed to awake several hours later with sharp abdominal pain which causes him to double up. The pain is soon relieved, and he sleeps again only to awaken a second time with a return of colic, and he frequently vomits. At first the pain is in the umbilical region, acute and spasmodic; later it becomes less acute but more continuous, and becomes localized in the right lower quadrant. The temperature, the pulse, and the respiration are normal, but there is always a slightly anxious expression. These attacks of appendical colic may have numerous remissions. Examination during attacks shows deep right iliae tenderness. A prompt operation is indicated; at operation the appendix presents some form of constriction and contains inspissated fecal material or a concretion and often gangrene.

There is also a type of mild acute appendicitis, probably embolic, secondary to an infection from sinusitis, tonsillitis, etc. The patient has malaise and nausea, a furred tongue, loss of appetite, and constipation with a very slight temperature. There is vague abdominal pain at the umbilicus which later becomes more or less localized in the right side. The patient may be in bed a day or two, at the end of which time the symptoms gradually clear up. Deep iliac tenderness can be obtained, and if an operation is performed, edema of the appendical wall is found. It is often these overlooked attacks which cause inflammatory reaction with subsequent fibrotic stricture of the appendix

There are numerous other combinations of symptoms neither so definite nor so suggestive of chronic appendicitis, but equally impor-A child who on automobile trips has nausea or tant to the child actively vomits, or who has had periodic attacks of vomiting, either repeated mild attacks often in the morning before breakfast or severe ones with associated acidosis, probably has chronic appendicitis. He may, however, never have had any abdominal pain. A white blood count with a nuclear shift may show slight irritative changes, as increase in rod nuclears, in addition to changes suggesting a more chronic inflammation, as lymphocytosis and monocytosis. An examination of the abdomen at the time of a vomiting attack frequently discovers deep that tenderness and less often right rectus rigidity. These patients are treated as a rule for an imbalance of the sympathetic nervous system causing reflex vomiting and spasticity of the colon, resulting in colicky pains and constipation. A roentgen ray

study of the gastrointestinal tract may occasionally disclose a partially filling appendix which does not empty in the normal time (only one case in this series), but, as a rule, roentgen rays are not conclusive except as evidence of spasticity of the colon. Roentgen ray examinations were not used in this series on account of the expense and the fact that the diagnosis could be made without their aid. It was also telt that the barium and bismuth retained would complicate convalescence following operation. It is necessary to proceed with extreme

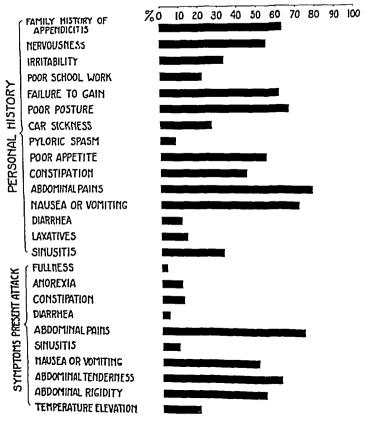


Chart 1 .- Symptomatology.

caution and observe these patients for some time and to rule out any involvement of the genitourinary tract, by urinalysis and roentgenograms if necessary, but when by a process of elimination focal infections are excluded, one is justified in making a diagnosis of mechanical lesions in or around the appendix. Diagnoses are largely based on a history of long-continued symptoms and by elimination rather than by physical findings.

There is another group of children with definite symptoms of chronic appendicitis; in these the blood count usually shows an eosinophilia.

with an average of 4 per cent. Most of these patients in our series had scatworms in the appendix and were completely relieved by appendectomy. This condition was first recognized in 1899 by Still<sup>7</sup> and has been lately reviewed by Margaret Warwick.<sup>8</sup>

Once a diagnosis is established, an immediate appendectomy is undoubtedly the only treatment. In cases in which a diagnosis of chronic or mild acute appendicitis is associated with a sinusitis or other upper respiratory infection, one should operate at once. It used

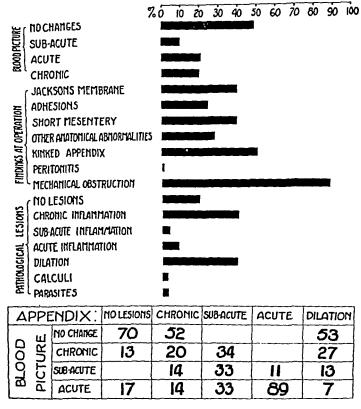


Chart 2 .- Blood picture and pathologic findings.

to be our custom to delay operation until the infection cleared up, but we found that severity of the appendical condition is greatly increased, and there is grave danger of a gangrenous appendix and peritonitis if operation is delayed. By use of tribrom-ethanol (avertin) and the post-operative use of 10 per cent carbon dioxide and 90 per cent oxygen we have had uniformly good results.

In only one of our series of 127 cases was it necessary to use drainage. That patient was first seen two days after the onset of acute symptoms. Recovery was complete in thirty-nine days.

The most constant symptoms in our cases were attacks of abdominal pain, generalized at first, later sometimes localized with associated nausea or vomiting. The most common physical finding was deep tenderness in the right iliac fossa.

Charts 1, 2, and 3 give the frequency of occurrence of the various symptoms, findings at operation, pathologic conditions, and the results.

The pathologist in cases of chronic appendicitis must examine the appendix not only for signs of chronic fibrosis and acute inflammatory changes but also for evidence of cystic dilatation as is shown in microscopic section by flattening out of the rugae and also by atrophic changes in the mucosa.

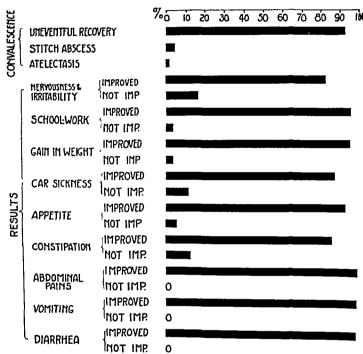


Chart 3 .- Postoperative course and results.

In an analysis of the Bryn Mawr Hospital pathologic records of acute appendicitis in adults, approximately 95 per cent showed evidences of preceding fecal retention and cystic dilatation.

#### CONCLUSIONS

1. In 127 consecutive cases of mechanical lesions affecting the appendix in childhood, the symptoms usually began at an early age in mild form and recurred over a long period, the most constant being recurring abdominal pain, frequently associated with vomiting and deep right iliac tenderness.

- 2. In addition to complete recovery and relief from symptoms in all cases following appendectomy, the children showed a very notable increase in weight.
- 3. The extrinsic causes of obstruction of the appendix predominated, often leading to obliteration of the lumen and retention of fecal material.
- 4. Approximately 95 per cent of adult appendices removed at the Bryn Mawr Hospital showed evidence of obliteration of the lumen with fecal retention preceding the terminal inflammatory attack.
- 5. By a careful diagnosis in childhood and early operation, nutrition and development could be made normal at this age period, and mortality could be minimized at all ages.

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# A STUDY OF THE BIRCH-HIRSCHFELD PHOTOMETRIC TEST FOR VITAMIN A DEFICIENCY

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VITAMIN A is one of the thirty-seven food substances essential for normal nutrition. A lack of this vitamin results in pathologic changes in many parts of the body. The most obvious changes are in the epithelial cells which tend to lose their columnar shape and become stratified. The occurrence of these changes in the conjunctiva and lacrymal glands results in the development of the eye condition known as xerophthalmia. This condition, however, develops only after an almost complete deprivation of vitamin A for many months.

Xerophthalmia is rarely encountered in the United States and Can-During the past ten years at the Hospital for Sick Children in Toronto, we have seen only one case of xerophthalmia out of 802.000 attendances at the hospital. Similar figures indicating the rarity of this condition have been obtained from Harriet Lane Home, Johns Hopkins Hospital, Baltimore; the Children's Hospital, St. Louis; Minnesota General Hospital, Minneapolis; the Children's Memorial Hospital, Chicago: the Massachusetts General Hospital, Massachusetts Eye and Ear Infirmary, and the Children's Hospital, Boston; and the Montreal General Hospital. Montreal.1 These findings are what one would expect when one considers the distribution of vitamin A in the foods ordinarily consumed. It is found in large amounts in the fats of dairy products. animal fats, liver, and egg yolk. Carotene, the precursor of vitamin A. is found in large amounts in spinach, chard, carrots, and many other vegetables and fruits. Vitamin A is probably the most widely and abundantly distributed of all the vitamins.

In harmony with this widespread and abundant distribution of vitamin A in foods is the absence of evidence of vitamin A deficiency at postmortem examination. At Boston, in the Children's Hospital, in 1,756 autopsies, keratinizing epithelial cells were demonstrated in only 15 patients.<sup>2</sup>

It is well recognized that night blindness may be caused by a lack of vitamin A. When this condition is present, the individual is unable to adjust his vision to decreasing amounts of light. The defect may be produced by a lesser deficiency of vitamin A than that necessary to cause

From the wards and laboratories of the Hospital for Sick Children and the Department of Paedlatries, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P.(C).

xerophthalmia. Demonstration of this defect, which can be present without any other obvious changes, might therefore indicate that the individual was suffering from a lack of vitamin A.

Reports have recently appeared in some European countries on the prevalence of night blindness.<sup>3</sup> Of much more interest and importance to us, however, are the reports of Jeans and Zentmire of Iowa City. These investigators found defective dark adaptation in 21 per cent of a group of children just admitted to the hospital.<sup>4</sup> In their more recent report of a survey of Iowa school children,<sup>5</sup> they found definitely subnormal dark adaptation in 26 per cent of the children from the rural districts, 53 per cent of the children from the villages, and no less than 56 to 79 per cent of the urban children, depending on their economic level. Furthermore, on the administration of vitamin A to 87 of these children with subnormal dark adaptation, they found either improvement or a return to the normal level in 84, or over 95 per cent.

These are most unexpected results. Although no details of the diets are given, it can be assumed that the diets are of the same standards as those used throughout most of the United States and Canada. Thus the work of Jeans and Zentmire would indicate that the average diet today does not contain an adequate amount of vitamin A.

The question of the adequacy of the supply of vitamin A is of such importance that we undertook an investigation using the instrument and technic as described by Jeans and Zentmire.<sup>4</sup>

The instrument used in making the test was a Birch-Hirschfeld No. 329 photometer obtained from Carl Zeiss, Inc. The photometer consisted of a metal tube 18 mm. in diameter with an electric light bulb in the end. At the other end of the cylinder there were in respective order, an opal glass, an iris diaphragm, and a second opal glass 40 mm. in diameter. The diaphragm was opened and closed by a lever with a scale marked with the diameter of the opening in millimeters. A metal disk, with five circles punched out, slid in a groove distal to the second opal glass. The holes were circular, 4 mm. in diameter. Four of the holes were situated in the form of a 2 cm. square. The fifth hole was in the center equidistant from all the others. In front of this was a Goldberg wedge, which is a glass slide with a uniformly increasing depth of opacity from one end to the other and marked off with a scale from 1 to 13, the numbers varying directly with the opaqueness.

The bulb in the metal cylinder was illuminated by a transformer connected to 110 volt circuit. The transformer stepped the voltage down to 3.5 in the light circuit. The source of light thus did not vary. The subject was placed in front of the photometer and observed the light from the bulb coming in the following order through opal glass, the iris diaphragm, opal glass, the fivepoint disk and the Goldberg wedge. The amount of light coming through varied directly with the size of the opening or scale reading of the diaphragm and inversely with the reading of the Goldberg wedge. Also because the wedge is graded from clearness to near opacity, the five points were not all equally visible. The end-point of the test was taken when the subject could definitely distinguish only three of the five points.

The examinations were carried out in a completely darkened room. The subject was placed with the head on a chin rest 24 inches from the photometer. The subject

faced a six-foot square-white screen placed at a distance of 40 inches from his eyes. Immediately behind the subject was a 150 watt electric light with a metal reflector which illuminated the white screen.

The subject, seated in the position described above, was directed to observe the middle of the screen for five minutes, estimated by the use of an interval timer. At the expiration of the time, the timer was again set for ten minutes. The lights were put out and the subject was directed to look at the photometer. He was asked to tell the number of points of light he could see. The Goldberg wedge was adjusted and the diaphragm opened or closed until the minimum amount of light was found at which the subject perceived constantly three of the five points of light. The instrument was covered for a few seconds with the hand to make sure that the subject was answering correctly. This is in accord with the technic described by Jeans and Zentmire.<sup>4</sup> They state, "The operator always confirmed the accuracy of an endpoint by covering the wedge with the palm of the hand for a few seconds in order to rest the patient's eyes and then by having the subject again report on the number of points of light constantly visible."

Jeans and Zentmire<sup>4</sup> found that normal persons gave readings with the wedge set at 7 and the diaphragm at 14 to 20 at the first test, i.e., immediately after the eyes have been exposed to the bright light. It would appear that our light source before being reduced by a wedge and the diaphragm was of lesser intensity than that used by Jeans and Zentmire, as very few of the individuals we tested gave an initial reading with the wedge set higher than 5 and the diaphragm at 14 to 20 mm.

The subject will require more light for the first reading if it is taken immediately rather than a moment or two later. Thus it is impossible to make duplicate determinations of the end-point of the first reading because during the first few seconds after the room is made dark the recovery or adaptation is extremely rapid to a certain point and then slowly approaches the level that it reaches at the end of the tenminute period in the dark. The latter level is the one which Jeans and Zentmire used to determine whether the adaptation was normal or not. They state that with their instrument the normal eye recovers to readings with the wedge set at 7 and the diaphragm at 3 to 6 mm., inclusive. In individual tests we confirmed that the second reading was constant by using different combinations of wedge and diaphragm settings which gave the same light values. At the end of the ten-minute interval the subject's ability to perceive does not vary as it does at the first test. Thus in considering the readings the one taken at the end of the ten-minute period is the important one. The smallest amount of light required by the subject after the period in the dark gives the greatest adaptation.

In the winter and spring of 1935, 163 subjects were tested for dark adaptation as outlined above. Eighteen of these were adults (laboratory staff and nurses), and 145 were ambulatory patients in hospital or attending the out-patient clinic. At this time we were interpreting our results in terms of the position of the Goldberg wedge and the size of the diaphragm opening. Because, as mentioned above, the instrumental readings obtained by us were in a different range from those of Jeans and Zentmire, we had to set our own normal level. We took the readings of 15 of the normal adults (laboratory workers and nurses) who were on a good dictary regime and used them as a standard. We decided that any reading with the wedge set at 7 or higher was normal. Using this standard, 53 of the subjects tested, or 32 per cent, showed poor dark adaptation. Twenty-eight of the group with poor adaptation to the

dark were given 2 teaspoonfuls of cod liver oil daily, and 18 of these, or 64 per cent. showed what we considered was improvement after a period of from two to six weeks' therapy. We believed that the above group were suffering from vitamin A deficiency and that we had confirmed the findings of Jeans and Zentmire.

Later while carrying out further tests it seemed to us that there was an overlapping of the light values with different wedge settings and size of opening of the diaphragm. The physics department of the University of Toronto very kindly measured with a photoelectric cell the amount of light that was being transmitted to the subject at all the positions of the wedge and diaphragm. The measurements were made using the center light spot. The calibrations are given arbitrarily, allowing 1,000 for the wedge setting of 1 and the diaphragm wide open. Thus in terms of this apparatus, with a wedge setting of 1, diaphragm 20 mm. (wide open) the light value was 1,000 and with a wedge setting of 13 and the diaphragm of 2 mm. the value was 0.9. (Table I.) Any amount of light between can be obtained by suitable settings of the wedge and the diaphragm. The constancy of the light source was further checked by testing the transformer circuit with a sensitive voltmeter. The fact that the variations in potential were negligible indicated that the amount of light emitted by the lamp in the photometer did not vary.

We applied this table to the findings made in the winter and spring of 1935. It was observed that our arbitrary normal range obtained from the fifteen adults varied from 37 to 136. These adults were all taking what had been considered to be adequate diets, and, if we use this spread of readings for normality, then very few of our original group had poor adaptation.

In order to determine the optimum light adaptation we decided to test a group of children who were receiving more than adequate amounts

TABLE I

Light values for the photometer with the various positions of the wedge and diaphragm. This table was estimated for us by the Department of Physics of the University of Toronto. They measured with a photoelectric cell the amount of light transmitted to the subject through the center hole of the 5 points of light.

D, II.4	1	2	3	-1	5	6	7	s	9	10	11	12	13
20	1000.0	722.0	513.0	364.0	258.0	187.0	136.0	100.0	77.0	57.0	45.0	33.0	24.0
18	994.0	717.0	510.0	362.0	256.0	186.0	135.0	99.4	76.5	56.6	44.7	32.8	23.9
16	986.0	712.0	506.0	359.0	254.0	184.0	134.0	[98.6]	75.9	56.2	44.4	32.5	23.6
1.4	956.0	690.0	490.0	348.0	247.0	179.0	130.0	95.6	73.6	54.5	43.0	31.6	23.0
12	807.0	583.0		294.0									
10	628.0	453.0	322.0	228.0	[163.0]	117,0	85.4						
S	1	325.0	231.0	164.0	1		1			25,6			
6	1	196.0	139.0		,		37.0			15.5			
4		102.0	72.2	51.4	36.4			14.1				4.7	
2	38.5	27.8	19.7	14.0	9.9	7.2	5.2	3.8	3.0	2.2	1.7	1.3	0,9

<sup>\*</sup>D refers to setting of diaphragm.

tw refers to setting of wedge.

of vitamin A. To do this we tested 64 normal children from six to sixteen years of age, receiving in their daily diet 30 to 35 ounces of milk, butter, meat, fruit, two vegetables other than potato, cereal and bread. This diet supplies large amounts of vitamin A. In addition, they were given daily, 21,000 units of vitamin A\* for a period of six weeks. It was found that this group required light values ranging from 19 to 258 for the test. The same children had been tested prior to the administration of the additional vitamin A and the spread of readings likewise was from 19 to 258. No difference was observed in the range of readings before or after the administration of the additional vitamin A. This is shown in Chart 1.

During the six-week period in which the additional vitamin A was being administered, the children were tested at biweekly intervals. In

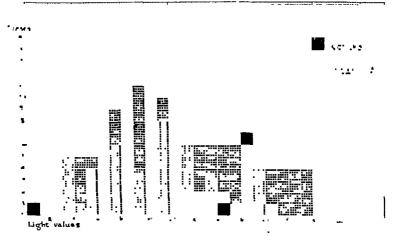


Chart 1.—Number of cases for the various readings for the test, before and after the administration of additional vitamin A.

Light value means the least amount of light necessary for the constant perception of the 3 points at the end of the ten-minute period in the dark. The cases are grouped with light values ranging from 0 to 20, 20 to 40, etc.

most cases the results obtained showed marked variations in the four tests on the same individual. A group of these selected at random are shown in Table II.

Because of the variability of the results we became concerned about the accuracy of the test. Dr. Walter W. Wright, chief of the ophthalmologic service of the Hospital for Sick Children, after examining the instrument and observing the technic of the test, stated that from his experience with other subjective eye tests with children he questioned the probability of obtaining reliable results.

In carrying out the test, the operator is entirely dependent on the veracity and personal reaction of the subject. If the subject reports

<sup>\*</sup>Ten drops of viosterol in halibut liver oil. Kindly supplied by Mead Johnson and Company.

seeing three points of light, unless the light is turned out or covered so as to be hidden, the operator must accept that as what the subject sees. We found it absolutely impossible to test children under six years of age because of this, as their imaginations took them into realms away above the number of points of light on the instrument.

In order to rule out as far as possible factors which are difficult to control in children, such as imagination and personal reaction of the subject, twelve adults, physicians and technicians, working in the labora-

TABLE II

Readings Obtained During the Administration of Additional Vitamin A\*

GIID Y DAM	PERIOD OF ADDITIONAL VITAMIN A										
SUBJECT	0	2 WEEKS	4 weeks	6 WEEKS							
I	19	85	45	37							
II	134	85	130	45							
$\mathbf{III}$	208	117	45	130							
IV	85	134	84	258							
v	61	179	130	110							
vr	37	37	130	110							
VII	130	85	85	130							
VIII	110	135	85	37							
IX	247	151	110	184							
X	85	136	179	26							

<sup>\*</sup>The lower the reading, the better the dark adaptation.

TABLE III

RECORDS OBTAINED FROM TESTS OF LABORATORY WORKERS AT APPROXIMATELY DAILY INTERVALS\*

SUBJECT	TEST	2	3	4	5	6	7	8	9	10	11	12	13	14
A B C D E F G H I J	116 70 116 26 84 37 254 208 84 184 186	163 70 50 84 163 50 208 208 247 70 151	116 116 36 37 184 26 228 163 50 184 117	208 36 151 85 70 50 208 116 50 84 151	116 186 50 26 116 26 116 163 247 117	179 151 84 50 187 50 179	163 84 26 50 117 26 151	179 151 50 26 208	50 179 50 37 50	85 179 26 50	84 179 50 26	85 151	84	50
L	116	151		101				}		1				

<sup>\*</sup>The lower the reading, the better the dark adaptation.

tory were tested daily for varying periods. There was no change made in the routine of these individuals. The record of the tests from these subjects is given in Table III. Two consistently required a small amount of light to perceive the points; 3 consistently required a large quantity; 4 varied from day to day; 2 improved and 1 became less adapted to the dark as time went on. Also the subjects would observe when the light was near the limit of perception, that they saw 3, 2, 0, 5, etc., points when the source was not varied in any respect. The statement was also

made that the lights were being moved. Our tests with adults showed wide variation for individual subjects, similar to the results obtained with the children.

It was pointed out to us that adaptation to the dark may be somewhat a matter of experience. Persons living in rural districts have little difficulty going about in the dark because they have good adaptation. However, the same individuals residing in urban centers for a period lose that ability and then will regain it when on a vacation in the country after a week or so.

#### CONCLUSIONS

In our hands the Birch-Hirschfeld photometer has been unsatisfactory for the estimation of small variations in dark adaptation, such as might be produced by vitamin A deficiency.

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### CARBON TETRACHLORIDE POISONING

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INSTANCES of carbon tetrachloride poisoning have been frequently described.<sup>1-4</sup> Without attempting a comprehensive review, we are reporting an additional case, partly because the drug was contained in a common household material, but principally because clinical discussions of the treatment of this intoxication have been rare.

#### USES FOR CARBON TETRACHLORIDE

Most instances of poisoning from this drug occur because of its use in certain fire extinguishers, in various cleansing solutions, and in the treatment of hookworm disease. The fact that its vapor is heavier than air makes it valuable to the fire fighter, but dangerous to the recipient of a "dry" shampoo who breathes the intoxicating fumes that settle around her face, or to one using the chemical as a grease remover inside a closed automobile. Poisoning due to absorption through the gastrointestinal tract has occurred chiefly in the treatment of hookworm disease.

#### PROPHYLAXIS

The Egyptian Board of Health in its wholesale treatment of villages for hookworm disease has found carbon tetrachloride intoxication occurring often enough with the therapeutic dose of 4 c.c. to warrant a routine set of precautions enforced within the temporary compounds where all treatments are given. The routine may be briefly outlined as follows: All persons who have recently taken alcohol are refused treatment. Ascaris infection also is considered a contraindication to the use of carbon tetrachloride because of the possibility of obstruction to its rapid excretion. All persons to be treated are placed on a high carbohydrate, low fat diet by advance agents. Immediately before the therapeutic dose of carbon tetrachloride, sugar in the form of molasses is given each patient. Following the administration of the carbon tetrachloride, each patient receives a saline cathartic. Patients may not leave the compound until the purge has proved effective. Those showing toxic symptoms are treated immediately with calcium and glucose.

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals.

#### PHARMACOLOGY

The drug is absorbed through the gastrointestinal tract, the lungs, or injured skin.<sup>7</sup> Overdosage may cause hemorrhages in the gastrointestinal mucosa, albuminous infiltration of the glomeruli of the kidneys, and central necrosis with cirrhosis or terminal acute yellow atrophy of the liver.<sup>5, 4</sup> Lipemia has been a frequent finding.<sup>3, 4</sup> Toxic symptoms progress through vomiting, stupor, temporary recovery, jaundice, fever, ambly opia, edema, anuria, hematuria, albuminuria, convulsions and coma, to death. Alcohol, fat, or protein in the diet increases the drug's toxicity.<sup>7, 9</sup> High carbohydrate and calcium intake reduces intoxication and frequently is associated with recovery.<sup>7, 10</sup>

Minot and Cutler<sup>11</sup> have pointed out a guanidinemia in carbon tetrachloride poisoning which they believe is responsible for interruption of carbohydrate metabolism. They believe that glucose is not resynthesized from lactic acid and that this results in both a hypoglycemia and an accumulation of lactic acid in the blood and its excretion in the urine. Finding that guanidine and calcium are antagonistic<sup>11</sup> and believing that calcium is necessary for activating the adrenal mechanism that normally compensates for a low blood sugar,<sup>10, 12</sup> Minot and Cutler feel that intravenous glucose becomes permanently effective in compensating for the hypoglycemia only when given with calcium

#### CASE REPORT

The two year old boy (weight 25 pounds) who stimulated our interest in this type of poisoning was brought in on April 9, 1935, two hours after swallowing 1 to 25 c.c. of the noninflammable cleaning fluid Energine (90 per cent carbon tetra chloride, 10 per cent hydrocarbon with petroleum base). 13\* He had vomited immediately and become drowsy. Physical examination on admission showed no ab normalities except stupoi and the odor of carbon tetrachloride about his mouth. The essential feature of his treatment, which started immediately, was the intensive administration of glucose and calcium with a minimal fat and protein intake. Milk and fruit juices were the only foods allowed. Parenteral fluids were given on each of the first six days of the intoxication. The details of treatment are given in Table I.

Within twelve hours he was up playing around the cib, seemingly normal. The second day he refused to eat, had a temperature of 104° F., and a urine containing a trace of albumin, 2 red blood cells, 2 white blood cells, and occasional granular casts in each high dry field of an uncentrifuged, voided specimen. The blood at this time contained 80 per cent hemoglobin (Tallqvist), with 4,500,000 normal red cells and 25,000 white cells per cubic millimeter; 95 per cent of the latter were polymorphonuclear. On each of the first three days he vomited twice and had 5 stools which, though watery yellow, contained no blood, and grew no typhoid or dysentery organisms when cultured.

On the third day he refused to eat and was irritable. The temperature rose again to 103° °C. (pulse 160), and at 6:00 °C.M., following a few generalized twitchings, he

<sup>\*</sup>This particular product carried no announcement on the label to indicate either its chemical or toxic nature

TABLE I

		CAL- CHUM LAC- TATE		55 55 55 55 55 55 55 55 55 55 55 55 55	55 gr.				15 gr.	15 gr.	15 gr.	15 gr.	15 gr.	15 gr.	15 gr.	10 Kr.
TUSC.   ORAL	ORAL	rruft Juice	800	1,100	200	250			009	009	Soft solid diet with whole milk from this					_
		SKIM	800				1,200 gav.	700 gav.	780	780	Soft diet whole from	poin				_
	MUSC.	10% LIVER CR EX- GLIVE TRACT					c		ıa		3					
(.0.)	INTRAMUSC.	10% ca al.r.c.					10	10								
THERAPY (IN C.C.	S.C.	NOR- MAL SA- LINE		300	300	350										-
THERA		PLAS-				140	:									-
	8.10	10% ca gruc.	15 01	10	01 06	1000	10 10	10								
	INTRAVENOUS	50% GLP: COSE			55			ig ig							-	
	LNI	20% al.n- cosi:			190	12 22 22	100	300								- -
		10% gru- cosn	200 200	200	200											
	CLINICAL STATE		Stupor in A.M. Lively in P.M.	Anorexiu	Listless in A.M. Convulsions and un-	Semiconatose Liver 1,5 cm. Slight jaundice	Semicomatose Liver 3 cm. Slight edema	Interested in sur- roundings Edema, ascites, anuría	Brighter Anuria, edema	Playing; voiding Liver at umbilicus	Playing Edenn and ascites less Liver 3 cm.	Sitting up		Liver 2 cm.	Liver 1 5 cm	וזואפו דים מוויי
	_	IC- TERIC INDEX					15	15	15		10					
		CHEO- RIDE M.				06	06	06	90							
CHEMISTRY OF THE BLOOD	CAL- CIUM MG. %	10.2		7.0	10.0		11.0							11.8	2	
	SE- RUM PROT. GM. %	6.8			3.5	1.4.5	6,5	£.5		4.5			5.8			
	N.P.N. RUM MG. % PROT. GM. %	27			£	09	19	89		88			200	9	2	
	°0, Vor.,	52			30	38		20		20					_	
		DAY OF DIS-	-	21	က	-14	13	9	2	တ	6	10	11	27	2 =	

suddenly became rigid, cyanotic, pulseless, and unconscious, breathing irregularly. Intravenous sodium luminal (1 gr.) was ineffective. Ether relaxed the rigidity and clonic twitchings slightly; after receiving 25 c.c. of 50 per cent glucose intravenously at 7:30 p.m., the extreme rigidity of his early attack relaxed; moderate opisthotonus and mild twitchings still remained at 11:30, when he received 120 c.c. of 20 per cent glucose with 20 c.c. of 10 per cent calcium gluconate intravenously. At this time the blood pressure was 100/78; there was no papilledema. Spinal fluid collected at this time was normal. After midnight he was completely relaxed.

During the fourth and fifth days he was semicomatose and was fed chiefly by gavage. The liver for the first time became palpable, increasing in size so rapidly that by the seventh day it was at the level of the umbilicus. There was never real jaundice. Peripheral edema, ascites, and anuria were the prominent clinical findings from the fifth to the eighth day. The urine continued to show cells, casts, and appreciable albumin until the ninth day; it was normal thereafter. By the end of the second week edema and ascites were gone; the boy was sitting up playing in bed and eating a soft solid diet enthusiastically. The liver receded slowly and at the time of discharge, three weeks after admission, was still 1 cm. below the costal margin.

Three months after discharge he was reexamined. His appetite was poor. He had not gained weight. The liver edge was not palpable. When given 25 gm. of galactose by mouth, he showed no reducing substance in the urine collected for the next six hours. Phthalein excretion was within normal limits and the nonprotein nitrogen at this time was 23 mg. per cent.

#### COMMENT

It would be presumptuous to attach much significance to the limited data represented by this case. Yet certain points are of interest.

In the presence of the low chlorides, a constant hematocrit (4.500.000 red cells per cubic millimeter on the fourth day), and a rising nonprotein nitrogen level, it could be assumed, according to the theories of Minot and Cutler, that the low CO2 was related to the accumulation of lactic acid in the blood. Whether the severe convulsive episode on the third day was due to hypoglycemia must remain uncertain, inasmuch as studies of the blood sugar were not made during the acute phase; the blood calcium just an hour before the attack was low enough to make it conceivable that tetany may have played a part. We could not help but be impressed by the possible significance of calcium and glucose in the treatment of this intoxication. In the presence of adequate hydration we felt that the urinary findings, anuria, and the nonprotein nitrogen represented definite renal injury. We wondered whether the abrupt fall in serum protein was due to liver damage or Liver extract was given because of certain evidence that it has a substitution value in instances of acute hepatic damage.14 Plasma was used in transfusion because of the low serum protein and adequate hematocrit.

Because there have been so few clinical reports of recovery from a severe poisoning by this drug and because the therapy or theories in-

volved are not well known, we are including in our report the following outline for the study and treatment of similar cases:

- a. Emergency gastric lavage; catharsis.
- b. Low fat, low protein, high carbohydrate diet.
- c. Calcium intake maintained at 0.5 gram intravenously, or 2.0 grams by mouth, daily."
- d. If vomiting is predominant, continuous intravenous drip (calcium gluconate, 5 per cent glucose, normal saline).
  - e. Parenteral fluids and transfusion as indicated.
- f. Studies of blood sugar, ('O2, nonprotein nitrogen, calcium, serum protein, fat, guanidine, and lactic acid.

#### SUMMARY

We have reported an instance of severe poisoning from carbon tetrachloride contained in a common household cleaning fluid and have emphasized certain forms of available therapy, notably the intensive use of calcium and glucose.

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<sup>\*</sup>One gram of calcium is contained in 1,000 c.c. milk, 10 gm. of calcium gluconate, 4 gm. of calcium lactate, or 3 gm. of calcium chloride.

## Correspondence

The Relation of Tuberculosis to Generalized Atypical "Tuberculosis" Adenitis—A Manifestation of Lymphogranulomatosis Benigna (Schaumann)

Dr. Torben K. With, Copenhagen, Denmark

In a recent number of THE JOURNAL OF PEDIATRICS, A. Wilmot Jacobsen in a paper, "Generalized Tuberculosis of the Lymph Nodes and Multiple Cystic Tuberculosis of the Bones," has reported what he claims to be a case of proved tuberculous disease in a child in good general condition, who failed repeatedly to react to large doses of tuberculin.

To his statement, "With the Mantoux test, except the false negative reactions during the acute stage of some of the febrile diseases and in moribund patients, and those with overwhelming infections . . ., we have never seen another case of proved tuberculosis in a child who persistently gave a negative tuberculin test," can be added that the same rule holds true for the adult as shown by Hart1 and Lichtenstein.2 This rule is founded on a vast material of clinical and pathologic studies and is of the greatest value to the clinician and to the pediatrist. As Jacobsen claims to have described a case which is an exception to this rule, his statement is of the greatest interest from the standpoint of the biology of tuberculosis. If his case is studied in the light of recent investigations, however, doubt arises that his case is a proved exception to the above mentioned rule. The reasons for this are the following. lymph gland enlargement in his two cases, as he states, are of the same characteristic type, both clinically and histologically, as seen in Boeck's sarcoid. The disease of skin and mucous membranes "sarcoid Boeck-Besnier," the osseous condition of "osteitis multiplex cystoides" of Jungling, the lymph gland swelling of the type mentioned above, together with certain forms of pulmonary disease and splenomegaly have been grouped together by Schaumann3 under the term "lymphogranulomatosis benigna" as manifestations of a general systemic disease with many points in common with Hodgkin's disease. The recent communications of Mylius and Schürmann,4 Pautrier, 5 Salvesen, 6 Kissmeyer, 7 Chevallier and Führer, 13 and Nielsen 14 may be referred to for the details of interpreting these conditions as manifestations of the same systemic disease. The etiology and pathogenesis of benign lymphogranulomatosis, as well as of Hodgkin's disease, are obscure. Some hold that it is a disease sui generis with its own etiology-an unknown infectious agent (Kissmeyer<sup>7</sup>); others hold that it is merely a syndrome—a mode of reaction to different agents as tuberculosis, leprosy, or lues (Dariers); while a large group of clinicians hold that the disease is a special form of tuberculosis with a very low allergic reaction ("positive anergie," Martenstein and Noll,9 of the Breslau Dermatological School).

Whatever may be the etiology, it is far from being proved as tuberculous in nature. Jacobsen states (p. 305), "It is reported that the tuberculin test may be negative in lupus pernio, Boeck's sarcoid, and osteitis multiplex cystoides, as for example in Jüngling's Cases 2, 3, 7 and 9. These, however, and most of the other similar cases in the literature, were tested by the relatively insensitive Pirquet method, and it is by no means assured that the intradermal tests with the stronger dilutions would likewise have failed to produce positive tests in these individuals."

The following data show that a complete lack of reaction is seen in about onethird of the cases. Martenstein and Nollo found 5 of 16 cases of lupus pernio and Boeck sarcoid negative to 0.1 mg. of tuberculin intracutaneously. Danbolt10 found 7 of 11 cases of Boeck's sarcoid negative with 5 to 50 mg. Bonnevie and With11 found 7 of 23 cases negative to 1 mg., and of these 4 also were negative when tested with 10 mg. In light of the extensive work of Hart1 this should be considered as a strong argument against the tuberculous nature of the disease.

If the cases of Jacobsen are reviewed in light of their findings, the following points may be considered.

- 1. The two children suffer from a typical benign lymphogranulomatosis. Case 1 of the glands, bones and lungs, Case 2 of the glands and lungs only.
- 2. Both children have been exposed to infection with the tubercle bacillus by the father who was at home with open pulmonary tuberculosis from July, 1930, to January, 1934.
  - 3. With these facts in view, the following explanation is at hand:

The first child with the strongly positive tuberculin reaction has besides her benign lymphogranulomatosis a tuberculosis which has nothing to do with her primary disease. The fact that she died after a couple of years from generalized tuberculosis has no influence on this statement. Tuberculosis has been reported several times as a complication which has been the cause of death in both benign and malignant lymphogranulomatosis.

It is to be noted in Case 2, with the negative tuberculin reaction, that the reactions were not performed after January, 1933, and the child did not die until May 31, 1934. In the interval, January, 1933, to May, 1934, she was at home at the same time as the father and had opportunity to be infected with tuberculosis. Moreover, the fact that she was infected with tuberculosis and died from tuberculous meningitis within this interval is in agreement with the findings of Wallgren and Nilson12 that meningitis follows as a rule a few months after primary infection. The question remains as to why she was infected so late, as she had been living with, and exposed to, the father previously. It may be answered that in an exposed family some children are infected early while others avoid infection for a long time (Hart1).

4. As this child, provided that the interpretation is correct, was not infected with tuberculosis at the time of the negative tuberculin reaction, the case is not contradictory to the doctrine of the absolute value of the negative tuberculin reaction.

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Remarks to the Foregoing Paper of Torben K. With, "The Relation of Tuberculosis to Generalized Tuberculous Adenitis—A Manifestation of Benign

Lymphogranulomatosis"

Kornel L. Terplan and A. Wilmot Jacobsen, Buffalo, N. Y.

The histologic diagnosis of the lymph nodes in both of the cases published by one of us (A. W. J.) and the postmortem examination in Case 1 were made by the other (K. L. T.). Therefore, we feel that we ought to comment jointly on the foregoing paper of Dr. Torben K. With, which is based solely on citations from the literature of cases more or less similar to ours. We feel that more emphasis should be placed upon the pathohistologic features than was done by Doctor With. however, we wish to note a distinct disagreement as to the nomenclature. There is a most unfortunate tendency in present-day medicine to create new names for combinations of pathologic lesions which heretofore have been known under less misleading simple descriptive terms. One of these new names is "benign lymphogranulomatosis." It was introduced by Schaumann1 to designate tuberculoid granulomas in lymph nodes, skin, bone marrow, lungs, and sometimes in tonsils, and probably also in the spleen and liver. The characteristic histologic feature in all these organs is typical epithelioid cell tubercle formation, usually with absence of caseation, although slight central necrosis may be present, especially in the lymph nodes. This name has not been adopted by pathologists. Mylius and Schürmann<sup>2</sup> speak of the same lesions in lymph nodes as "universal tuberculous large cellular hyperplasia." They call attention to the later stages with hyaline sclerosis instead of caseation and calcification. They consider these lesions as a peculiar form of atypical tuberculosis, identical with the systemic large cellular hyperplasia described long ago by This hyperplastic type of lymph node tuberculosis is well known to all Some of them prefer the term "fungoid," designating tuberculous granulation tissue without caseation.

In discussing the etiology of "benign lymphogranulomatosis," Doctor With fails to mention that Schaumann,1,3 who originated this term, and also Schürmann and Mylius, interpret these lesions as atypical tuberculosis in an etiologic sense. causative agent in their opinion is a tuberculous virus. Schaumann tried to explain the absence of the tuberculin reaction by a state of anergy or a sensibility to tuberculin. We wish to call attention to the discussion of Schürmann and Mylius of their own cases, one of which showed a combination of tuberculous lymph node hyperplasia and ordinary progressive tuberculosis of the lungs. They state that "the negative reaction to tuberculin in pure cases of tuberculous lymph node hyperplasia should not impress us as being so strange when we consider the entire histologic picture, especially the absence of caseation. However, behind this symptom (i.e., the negative reaction) there are more problems hidden, which at the present time cannot be answered." These authors discuss further the different possible combinations of the noncascating tuberculous hyperplasia with the ordinary tuberculosis. two varieties may appear simultaneously, or a more caseating type may complicate a mere hyperplastic tuberculosis at a certain time which at postmortem examination may be estimated from the anatomic findings. This latter type possibly could be produced by two different tuberculous viruses. In most cases, however, it is, according to Schürmann and Mylius, impossible to learn anything certain about the time at which caseating tuberculous processes may appear in a patient suffering from tuberculous lymph node hyperplasia. On the other hand, in their opinion, this combination of the caseating and noncaseating types especially suggests the tuberculous etiology of the epithelioid cell hyperplasia in lymph nodes (so-called "benign lymphogranulomatosis'').

If as careful an observer as Schürmann admits the difficulty inherent in any attempt to analyze these cases of combined atypical and ordinary caseating tubercu-

losis in exact pathogenetic and etiologic terms, it is rather surprising to see the readiness of Doctor With to explain either the presence or the absence of the tuber culin reaction in our two cases. Doctor With bases his discussion on the assumption that the noncasenting or fungoid type of lymph node tuberculosis is not tuberculosis at all in an etiologic sense and that in both of our cases there were two different diseases which had nothing to do with each other. The literature which Doctor With himself quoted, especially the papers of Schaumann, and Schurmann and Mylius, suggests strongly that his interpretation is not necessarily correct. How can be feel sure that the benign lymphogranulomatosis was the "primary disease" and that only later as indicated by the positive tuberculin reaction a real tuberculous infection occurred? How did this "primary disease" enter the body? There was ample op portunity for tuberculous infection in the home of this negro family through all the years in which the two children were seen. The term "benign lymphogranulomatosis" was not used in our paper for reasons mentioned herein, just as Schurmann and Mylius, like many other pathologists, prefer the term "atypical lymph node tubercu losis" As to the etiology, in addition to Schaumann, and Schurmann and Mylius, Beintema4 and Jadassohn5 speak of tuberculoids. There are, of course, other dermatologists, especially of the French school, who do not feel that epithelioid cell granulomas in the skin and lymph nodes are tuberculous in nature, among these especially Pautrier.6 However, to introduce still another designation for this syn drome, as Pautrier does in speaking of "reticulo endotheliose," seems to us inappro priate masmuch as the term is already markedly overburdened and used for entirely unrelated diseases.

We strongly recommend discarding the term "benigh lymphogranulomatosis," as it has proved to be confusing, especially when used to suggest a relationship to tuberculosis similar to that borne by Hodgkin's disease. Indeed it inevitably implies such a similarity, as in many Europe in countries the term "lymphogranulomatosis" is used synonymously with Hodgkin's disease, which condition in a high percentage of cases is entirely unassociated with tuberculosis. With regard to this question, we might refer to the paper by one of us dealing with the nature, pathogenesis and etiology of Hodgkin's disease

From the postmortem findings in our first case it is clear that the tuberculous infection occurred several years previous to death. Several calcified foci were found in the parenchyma of the lungs. When and why at a later time the picture of tuber culous peritonitis and caseating bronchogenic spread in the lungs was brought about is just as difficult to explain as in so many other cases of chronic tuberculosis in children and adults. The entire complex question of evogenous reinfection or endogenous exacerbation should be carefully examined in all cases of this type Inasmuch as in our second case a complete postmortem examination was not per formed, we would prefer not to comment on the relation of the progressive tubercu lous lesion terminating in tuberculous meningitis to the tuberculous lymph node hyperplasia. There is, however, no reason to assume, as Doctor With does, that we are dealing with a recent tuberculous infection, which resulted in tuberculous meningitis. The first infection with tubercle breilli may have occurred several years previous to death in this case just as well as in the first one To the statement of Doctor With, based on a quotation of Wallgren and Nilson that tuberculous meningitis follows as a rule a few months after the primary infection, which he uses to prove the recent nature of the tuberculous infection in Case 2, there is a large number of exceptions in children and adults. We could cite from our own material several postmortem protocols proving that tuberculous meningitis is found in children and adults with entirely stony tuberculous complexes

The fact that we do not understand the tuberculin reaction in the individually different types of tuberculous tissue processes, especially in the purely hyperplastic type, should make us very careful not to arbitrarily dismiss the possibility of tubercu

losis on the evidence of a negative tuberculin test alone. All the environmental factors, the family history, signs of tuberculous infection in all children, linked with the anatomic histologic findings in both of our cases speak strongly for a common The histologic picture is that of atypical epithelioid cell tuberculous etiology. hyperplasia. There is so far no other etiologic agent known which can bring about a universal tuberculous lymph node hyperplasia with epithelioid cells and Langhans' giant cells, with or without slight central necrosis, except the tubercle bacillus or a tuberculous virus in a wider sense.

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## Critical Review

#### TUBERCULOSIS IN CHILDREN

LEE FORREST HILL, M.D. DES MOINES. IOWA

THE most comprehensive survey ever undertaken of the facilities for caring for tuberculous patients in the United States has been completed by the Council on Medical Education and Hospitals of the American Medical Association and was fully reported in the December 7, 1935, issue of the Journal of the American Medical Association;1 471 sanatoriums, 740 tuberculosis departments of hospitals, and 29 preventoriums provided the statistical data upon which the report is based. The total capacity for tuberculosis is 95,198 beds: 64,997 in the sanatoriums, 28,534 in the tuberculosis departments, and 1,667 in the pre-The total replacement value of the tuberculosis ventorium group. institutions is estimated at approximately \$328,937,777.36, or a general average of \$3,455.30 per bed. The annual cost of the tuberculosis hospitalization in the United States exceeds \$70,000,000. The average cost of maintaining a tuberculous patient in the sanatoriums is \$2.37 a day; in the tuberculosis department, \$2.95; and in the preventoriums, \$1.39.

More pertinent for the purposes of this review is that part of the report which deals with children. A total of 11,647 beds are available for this group of patients in all the tuberculosis institutions. Of these the sanatoriums provide 9,036; the tuberculosis departments of hospitals, 944; and the preventoriums, 1,667. All together, 230 sanatoriums admit children. Over half of the sanatoriums admitting childhood tuberculosis also admit children with pulmonary tuberculosis of the adult type. The figures given for admissions to the tuberculosis sanatoriums show that of a total of 12,629 children, 1,191 had adult type tuberculosis; 6.659, the childhood type; 824 had extrapulmonary lesions; 3,236 were nontuberculous; and 701 were unclassified. Sixteen of the twenty-nine preventoriums reported 2,479 patients admitted, of whom 12 had the adult type tuberculosis; 424, the childhood type; 24 had extrapulmonary lesions; 1,326 were nontuberculous; and The report further states that many of the 693 were unclassified. sanatoriums admitting children have a waiting list for adults and properly questions the wisdom of such a procedure, pointing out that the prime objective in tuberculosis control is the isolation of tuberculous patients who give off tubercle bacilli. For the most part, the report indicates that the children in tuberculosis institutions received adequate protection from "open" cases of tuberculosis, but that in some there were opportunities for contact between adult patients and children, and in a few sanatoriums it was observed that children with pulmonary tuberculosis were hospitalized together with other children in the preventorium unit.

It is rather surprising to learn that over 37,000 tuberculous patients were admitted to general hospitals in a one-year period (1934). doubtedly the majority of these institutions provide adequate segregation facilities, but it is a fair surmise that there are many thousand other unrecognized tuberculous patients admitted to hospitals in general who are a source of contagion for other patients, nurses, doctors, and attendarts. That such a surmise is correct is attested by observations on nurses and medical students among whom the percentage of positive reactors to tuberculin is relatively low at the beginning of training, but approaches 100 per cent by the time the training period has been completed. The medical profession as a whole still pays too little attention to the communicability of tuberculosis. The time is not far distant when the same contagious technic will be applied to the care of tuberculosis as is now applied to diphtheria and scarlet fever. In fact it is not improbable that within a few years it will have become the custom in many of our hospitals to require satisfactory evidence of the absence of tuberculosis in a communicable form before the admission of the patient to the general wards. This could be accomplished at slight expense by means of routine fluoroscopy for all patients over ten years of age. Such a procedure should be but little more troublesome than the requirement of throat cultures and vaginal smears enforced in many pediatric departments and should reduce the hazard to doctors and nurses, as well as benefit the patient. If it were carried out in obstetrical departments, loss of life among infants due to fatal forms of tuberculosis could be materially reduced.

Another point worth dwelling on briefly and which the report brings up is the matter of institutional care of children who are in contact with tuberculosis in their homes or who have only the first infection type of tuberculosis. From the report it will be seen that there were many such admitted to sanatoriums and preventoriums. Obviously a considerable sum of money was involved in the care of these children. Was it worth it, or could this money have been spent to better purpose in other ways?

Myers<sup>2, 3</sup> believes that knowledge gained from years of observation of large numbers of children with primary tuberculosis has amply demonstrated that these children do not need treatment in sanatoriums, preventoriums, special schools, fresh air classrooms, or summer camps, to heal their tuberculous foci. Treatment in such institutions neither hastens the healing process nor makes it more complete than that which occurs in the child's own or a foster home. If the child remains in his own home, it is of course desirable that the infecting source be removed. He cites as substantiating evidence of his opinion the results of treatment in 155 children who were observed from the time the disease was in the acute inflammatory stage until lime or fibrous strands were deposited in sufficient quantity so that they could be visualized in the x-ray film. Nineteen were treated in sanatoriums; 50 in the Lymanhurst school; and 86 in their homes. Among 136 whom it was possible to trace, no difference could be seen in the course of the disease, whether the children were treated as strict bed patients, sent to a special school, or remained as active as any normal child is in the home. Consequently, Lymanhurst has discontinued its treatment division and has diverted its funds into other channels of tuberculosis control.

Nor "have we been able," states Myers.2 "to obtain any evidence to show that hospitalization, special schools, summer camps, or any other form of treatment except breaking contact with tubercle bacilli has any influence upon the later development of reinfection type of disease." Again the point should be made that the admission of a child to a tuberculosis institution does not insure that contact with tubercle bacilli will be prevented. On the contrary, the opportunities may actually be increased.

In addition to the argument that institutional treatment of first infection tuberculosis is unnecessary, the proponents of this line of reasoning draw attention to its futility. For instance, Myers² speaks of the situation at Lymanhurst in Minneapolis, where there were estimated to be 20,000 children infected with tuberculosis and 70,000 others who needed protection from infection. The capacity for treatment at Lymanhurst was 175. Certainly the expenditure of funds for the care of this small number in view of the much larger problem accomplished very little.

Consequently, the money formerly used to maintain these children in the preventorium unit is now employed to do tuberculin testing on large groups of children; to search out and segregate the source of contamination of the positive reactors, thus making not only the child in his own home safe, but also giving protection to the rest of the community; and finally to follow up the adolescent positive reactors by frequent x-ray examinations in order to detect the reinfection form of tuberculosis sufficiently early to institute therapeutic measures aimed at arrest of the process and prevention of the victim's in turn becoming a spreader of bacilli. Such a program would seem to yield far greater returns, in terms of tuberculosis control, for the financial outlay involved, than the preventorium method. According to Stewart, similar changes to those going on at Lymanhurst are now in process of development elsewhere.

Pastor,<sup>5</sup> in discussing the fight against tuberculosis in Puerto Rico, advances further arguments against the value of the preventorium in his locality. He found it cost as much to maintain a well child in a preventorium as to support a tuberculous patient in a sanatorium. Taking the child away from the home to protect him from contagion is an expensive and impractical procedure. It is far easier, more effective, and less costly to send away the focus of contagion, leaving the rest of the family at home. Beds in sanatoriums should be for sick persons who are potential sources of contamination. He suggests that tuberculosis workers adopt the slogan, "Make every home a preventorium."

Moreover, if protection of the infected child is to be effective, it must not be limited to a few months of institutional care, where the child merely gains a few pounds of weight only to lose it when he returns to his poor home, but it must extend over a period of years into adult life, since most childhood infections that do light up do not become activated until the age of puberty or thereafter. "By keeping the home free from foci of contagion, raising its standards, educating parents, and affording facilities for systematic clinical supervision of contacts, we could probably achieve more in the prevention of tuberculosis than has been achieved by all the preventoria of the past and of the present," says Pastor.

Hawes,6 on the other hand, is convinced that properly run preventoriums and summer camps are decidedly worth while in the campaign against tuberculosis. On the basis of fifteen years' experience with the Prendergast preventorium in Boston, he states that he knows "of no more effective way in which our present knowledge of tuberculosis may be extended than by means of the preventorium and the summer camp, providing that active and practical measures are used to educate not only the children themselves in the principles of health and hygiene, but also their parents and other members of their families, and likewise the general public, including physicians, nurses, and social workers, as well as the laity." As proof of the value of the work that may be done in a preventorium like Prendergast, he compares 705 children admitted to that institution in the decade from 1922 to 1932, with 705 other children with similar tuberculosis experience who had not been to Prendergast but had been taken care of in their homes either by family physicians or doctors and nurses from a health clinic. In the Prendergast group of children it was found that only one had subsequently died of tuberculosis, and only three had developed the disease in clinical form, whereas in the other group ten had died from tuberculosis and forty had developed the disease.

The figures presented by Hawes represent a striking difference in morbidity and mortality in favor of the preventorium group of children. One is inclined to think the efforts of breaking contact in the nonpreventorium group could not have been very effective. However, if further observation of comparable groups continues to show similar results, then certainly a powerful argument exists justifying pre-

ventorium residence.

#### CONCEPTS OF TUBERCULOSIS

Fifteen years of longitudinal study of many thousands of children for tuberculosis have enabled the Lymanhurst workers to form a concept of the evolutionary course of tuberculosis as it occurs in the human being from the beginning of the first seeding of tubercle bacilli on normal preallergic tissues to disabling disease or death from chronic destructive pulmonary tuberculosis. Their observations have been presented so succinctly and so convincingly that probably the rank and file of physicians in this country are in agreement with their views. However, there is a substantial number of other wellknown workers in the tuberculosis field, whose opinions command respect, who differ with some of the interpretations of the Lymanhurst group. Controversial questions center largely about the significance of allergy and immunity; about racial and individual resistance; about the reason for the infrequent appearance of phthisis before the age of ten; about the effect of the massiveness of the infecting dose of organisms; about the relative importance of endogenous and exogenous sources in causing reinfections; about the part played by a first infection in preventing or predisposing to later reinfection types of tuberculosis; and finally about whether it is more desirable to enter adolescent and adult years with a negative or with a positive reaction to tuberculin.

The impression should not be gained that these are the only problems remaining for solution in tuberculosis, but merely, that at the present time, they are the questions receiving most attention in the literature on tuberculosis in children. In last year's review<sup>7</sup> the Lymanhurst interpretation of tuberculosis was presented in considerable detail. It may be advantageous to restate the high points of that concept here, to add further contributions which have been made during the year, and then to consider some of the views which approach the problem from other angles.

Recent articles by Myers and his associates' and by Stewart', summarize their ideas on the evolutionary course of tuberculosis. According to these authors, there are two general types of tuberculosis, the first infection type and the reinfection type, both caused by the same organism, but differing so markedly in almost every other respect as to suggest they are separate disease entities. Concerning this statement there is almost universal agreement among tuberculosis workers, but it may be said to be unique in this respect.

First infection tuberculosis results when tubercle bacilli are seeded on nonallergic tissues, whereas reinfection type tuberculosis requires for its development that the tissues be allergic to tuberculoprotein when the bacilli are implanted. The one essential determining difference between the two types, therefore, is allergy, and this holds true regardless of the age of the patient as will be brought out later. First infection may occur in the lungs, abdomen, or cervical region, and the foci may be single or multiple, large or small. It is probable, too, that from the primary focus during the preallergic period bacilli are disseminated like particulate matter to various organs of the body thus setting up numerous other foci which may be of importance in the development of subsequent reinfection forms of tuberculosis. is not available, but it is possible that this is the mechanism involved in the formation of the foci in the brain, from which bacilli escape to produce meningitis as has been shown by Rich and McCordock. Similarly, it is conceivable that bone and joint tuberculosis or renal tuberculosis may arise from hematogenous "rests" deposited in these structures at the time of the primary infection, which do not become activated for months or years afterward.

During the preallergic stage following the initial infection, symptoms and physical signs are completely absent, and diagnosis of the condition is impossible except by recovery of organisms by gastric lavage. However, Myers states that he is at present engaged in a study to determine whether or not there occurs in the peripheral blood sufficient of the leucocytic, monocytic, and lymphocytic activity occasioned by tubercle formation to be of diagnostic significance. The difficulty in knowing the exact time infection takes place in accidental exposures obviously stands in the way of the practicability of this means of early diagnosis.

In from three to seven weeks sensitivity develops, and coinciding with it perifocal allergic reactions may occur about some favorably situated primary pulmonary lesions so that they can be visualized in x-ray films. Many of these lesions acquire central areas of cascation at the time allergy appears, and a transitory fever of varying intensity and duration may occur during this period. However, only a small percentage of the children who become infected with tubercle bacilli for the first time develop lesions which are large enough to cast shadows in the x-ray film. In those who do develop such lesions it is believed that the defense mechanism of the body has not adequately surrounded the foci of bacilli before allergy appears, thus permitting

a diffusion of tuberculoprotein into adjacent tissues which causes the collateral inflammation visible roentgenologically. In the majority of cases the defense mechanism is adequate, and no collateral inflammation occurs about the primary focus, which fact explains why the x-ray film is negative in such a high percentage of positive reactors. Cases of both types have been followed by serial x-ray study, and in both, at some subsequent time, calcium deposits have been observed to make their appearance.

To date 210 children with proved first infection tuberculosis (131 with pulmonary infiltration demonstrable roentgenologically) have been observed by the Lymanhurst group, and have been followed by serial x-ray study. One of these children died of tuberculous meningitis approximately a year after he had been sent to a first class sanatorium. All the others followed a surprisingly uniform course. For weeks or months no gross change occurred in the extent of the pulmonary infiltration. There then occurred a gradual progressive process of resolution which led in the course of months to two or three years, to a complete roentgenologic disappearance of the lesions, or to their reduction to trivial fibrosed scars or to calcium deposits. "The changes observed in these lesions," says Stewart, "illustrate on a large scale the evolution of all primary varieties of the disease, regardless of where the pathology is situated and irrespective of whether the lesions are large or small." Furthermore, this same course has been observed to follow when first infections have occurred in adults, thus disproving, in the opinion of the Lymanhurst authors. the popular belief that an adult who becomes infected for the first time nearly always develops rapidly progressive clinical tuberculosis. Also negro, Mexican, and Indian children have been observed who have resolved their first infections in the same manner as white children. This ability on the part of children of these races throws doubt upon the alleged destructiveness of primary infections in the adult members of such races. Such destructive forms are more likely to be reinfections.

In the centers of the calcareous foci virulent tubercle bacilli may remain alive throughout the lifetime of the individual, thus accounting for persisting sensitivity. Attempts on the part of nature to remove the calcified areas as foreign bodies by ossification and revascularization provide an opportunity for the freed bacilli to gain access to the blood stream, and hence to the potential establishment of reinfection forms of tuberculosis of endogenous origin.

According to the Lymanhurst interpretation, the term "reinfection type of tuberculosis" is applied to those forms of tuberculosis which develop as new lesions or which extend beyond the limits of the original primary pathology when such lesions develop after tuberculin sensitivity has become established, regardless of whether the complications occur a few weeks or many months after the first infection form of the disease was acquired. Thus tuberculous meningitis, miliary tuberculosis, tuberculous pleurisy with effusion, and bone and joint tuberculosis, as well as phthisis are all regarded as reinfection forms of the disease.

First infection tuberculosis is considered to be a relatively benign disease, which almost invariably undergoes resolution without any special form of treatment, whereas reinfection tuberculosis accounts for practically all of the serious disease manifestations and deaths. However, primary tuberculosis is not, in the opinion of these authors, a beneficial experience to the host in that it tends to create a degree of immunity against the later development of serious tuberculous disease. On the contrary, they consider it a double liability: first, because it is responsible for the production of allergy to tuberculoprotein which is an essential antecedent to the development of reinfection tuberculosis; and second, because its original foci may be the source of the bacillary metastasis which results in early or late, acute or chronic forms of reinfection tuberculosis. In substantiation of this viewpoint, they call attention to the failure of first infections to create immunity sufficient to protect against tuberculous meningitis. bone and joint tuberculosis, and miliary tuberculosis, and point out that an immunizing procedure for other communicable diseases which was equally ineffective would hardly be acceptable. Moreover, they have shown that phthisis is never the result of a first infection but is always the product of a reinfection. In a group of 131 children with pneumonic lesions of first infection type not one developed into phthisis, but in a group of 54 tuberculin-sensitive patients who developed reinfection pneumonic infiltrations years after they acquired their primary infections, the invariable outcome has been progressive disease typical of phthisis, resulting in death for a fourth of the group, and in advanced disease for some of the others.

First infection tuberculosis, then, in the Lymanhurst interpretation, is the introductory state of all clinical varieties of the disease. It not only fails as an immunizing force to protect against the subsequent acquisition of phthisis, but actually contributes the essential factor which makes possible its development. The prognosis as regards tuberculosis for patients who contract a first infection cannot be determined for many years. A few of them, but not nearly so many as was once thought, will develop acute forms of reinfection tuberculosis, such as meningitis, and miliary disease; a few will acquire tuberculosis of the bones and joints and of various viscera; and from 10 to 20 per cent of this group of tuberculin-sensitive children are destined later to develop chronic pulmonary tuberculosis either from endogenous or exogenous sources. A positive tuberculin reaction, then, in the opinion of the Lymanhurst workers, can only be considered as a distinct liability to the child entering the age group susceptible to phthisis. The conquest of tuberculosis for the human race is to be achieved through epidemiologic and preventive measures, as it has been for the bovine family, rather than by widespread tubercularization and survival of the fittest.

Attention may now be turned to a consideration of some of the contributions appearing in the literature of the past year which attempt to shed further light on why tuberculosis behaves as it does in human beings. Myers<sup>10</sup> draws upon the results obtained by numerous workers in animal experimentation to offer a reasonable explanation for the observed benignity of first infections. He refers to the work of Vorwald<sup>11</sup> who found that within an hour after the intravenous injection of virulent tubercle bacilli into rabbits polymorphonuclear leucocytes could be demonstrated in alveolar capillaries grouped about collections of tubercle bacilli, some of which had already been phagocytosed. Within three hours mononuclear exudate cells had

collected in the walls of the capillaries surrounding the bacillus-laden polymorphonuclear leucocytes, and within a few hours more the exudate cells had taken on the function of phagocytosing tubercle bacilli and disintegrating leucocytes. Typical tubercle formation was evident at the end of a day. At the end of a week the typical predominating cells were the mononuclears, some of which could be recognized as epithelioid cells. By the end of a month the tubercles were macroscopic in size. Lymphocytes and plasma cells were concentrated about the tubercles, and central cascation was observed in some of the tubercles in which tubercle bacilli were found free. "This focalization and walling off of bacteria before sensitization appears may be an important factor in making primary tuberculosis a benign disease," states Myers.

He cites the studies of Lemon and Montgomery,12 who show that the tissues of rabbits at first react with a nonspecific form of inflammation to bovine tubercle bacilli injected into the pleural space, as though they were foreign bodies of particulate type. The fluid and cellular parts of the resultant effusion are promptly resorbed, carrying with them the particulate material, which has been phagocytosed, and depositing it in regional lymph nodes and in remote organs. This preallergic nonspecific reaction of tissues is further illustrated by the experiments of Lemon and Feldman, 13 who compared the tissue reactions produced when particles of silica and virulent avian tubercle bacilli were introduced into the trachea of different rabbits. The early cellular reactions which developed about the particles of silica were essentially the same as those which appeared about the tubercle bacilli. Later, however, with the advent of sensitivity and in response to growth and multiplication of bacilli, the type of inflammation became specific in the tuberculous animals. Myers refers to various other studies which demonstrate that the injection of virulent tubercle bacilli into animals previously rendered allergic to tuberculin is followed by a more rapid and severe type of inflammation than that which results from an initial injection. For instance, Long14 has shown that small doses of tubercle bacilli and their products have no immediate effect upon the cells of the testes of normal guinea pigs. However, when equivalent doses of tubercle bacilli are injected into the testes of animals which have previously been sensitized, degeneration of the cells begins almost immediately. And again Stewart, Long, and Bradley, 15 and Holst 16 found that leucocytes from animals which had not been infected with tubercle bacilli were not harmed when they were brought in contact with tuberculin, whereas leucocytes from animals with tuberculosis were definitely damaged under the same treatment. Also Seibert<sup>17</sup> sensitized normal guinea pigs and showed that a high degree of sensitiveness conferred no immunity or increased resistance to tubercle bacilli. On the contrary, it seemed to hasten and extend the lesion and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals.

The events leading to the development of sensitivity of tissues in animals (and the reaction in humans is believed similar) following an initial infection with tubercle bacilli are described by Myers. "The first defense is offered by the neutrophiles when they phagocytose the tubercle bacilli in the blood stream. However, this defense is soon overcome, probably because of tuberculopolysaccharid which is toxic

to neutrophiles. These sluggish or dead cells containing tubercle bacilli accumulate even to the point of completely obstructing some capillaries, thus focalizing tubercle bacilli. The next line of defense consists of monocytes which engulf the disintegrating neutrophiles, but a tuberculophosphatid apparently is partially responsible for the early conversion of the monocytes into epithelioid cells. Although some tubercle bacilli apparently are killed by the epithelioid cells, others not only live, but also multiply. From the dead and disintegrating bacilli, as well as from those proliferating, more products are given off which stimulate the local cells. The waxes cause a proliferation of fibroblasts, and the acctone-soluble fat stimulates proliferation of all connective tissue cells. In due time, tuberculoprotein results in an outpouring of plasma about the lesion and later causes sensitization of the body to such an extent that it can be detected by the tuberculin test."

Thus, animal experimentation has been employed to show that a quick "walling off" of tubercle bacilli occurs following first infection, that no differentiation is made in tissue reaction between inanimate particulate material and tubercle bacilli until sensitivity occurs, and that tissue sensitivity is responsible for the development of specific destructive lesions. Correlating these findings with observations made on human beings Myers states, "The entire early development of tuberculosis occurs in the human body without symptoms, abnormal physical signs, or x-ray findings. In many cases, apparently the tubercle becomes fibrosed, and no significant destruction of tissue oc-In my observations on large numbers of students of nursing and medicine who developed the first infection type of tuberculosis after exposure to patients. I have never seen one who presented any symptoms before the tissues were sensitized. Moreover, I have seen none who presented symptoms subsequently except those who developed reinfection tuberculosis, such as pleurisy with effusion, peritonitis, destructive pulmonary disease, etc."

Burke<sup>18, 19</sup> records an interesting study in animal experimentation, in which he produced primary and reinfection types of tuberculosis in rabbits and studied the resulting lesions by serial roentgenology, by roentgenograms of the excised lungs, and by pathologic examination.

The primary pulmonary tuberculosis produced in rabbits by the intratracheal injection of 1 mg. of virulent tubercle bacilli was comparable in many ways to primary pulmonary tuberculosis in children. The animals, like children with this type of tuberculous infection, were not ill and had no fever during the early progressive phases of the disease. The first roentgenograms to reveal shadows were those taken between the tenth and seventeenth days. The largest shadows were usually observed in the second month. Some of the films failed to show any shadows after the first three months, and commonly films made during the third and fourth months showed fewer and smaller shadows. In other instances, the shadows became dense and discrete and, having reached this stage, changed little during a period of years.

Both the roentgenograms taken during life and those of excised lungs failed in many instances to portray a true picture of the extent and location of disease demonstrable at pathologic examination.

Examination of the lungs of rabbits killed in later periods gave the author an unusual opportunity to observe successive stages in the

healing of primary pulmonary tuberculosis. In seven of the twelve rabbits killed between the eighth month and fourth year the lungs and paratracheal lymph nodes showed no evidence of disease. Some of the lungs showed various stages in the healing of tuberculous lesions by resolution, fibrosis, and calcification. Cavities were found in the lungs of only five of the thirty-five animals killed between the end of the first month and the end of the fourth year. Caseous foci were observed to be small, differing in this respect from those seen in the animals with reinfection tuberculosis.

In the second part of his experiment Burke sensitized rabbits by injecting avirulent tubercle bacilli in the groin, and produced reinfection tuberculosis by subsequent injections of 1 mg. of virulent tubercle bacilli The disease thus produced was comparable in many ways to the adult type of reinfection tuberculosis seen in man. Unlike the rabbits with primary pulmonary tuberculosis, these became ill for a week or two following the injections, and many had fever. Abnormal shadows were found in the roentgenograms as early as the first day, and usually reached their largest proportions during the second week. However, no shadow or combination of shadows was found in the chest roentgenograms or in the roentgenograms of the excised lungs which served to differentiate the lesions of reinfection from primary. Caseous foci were larger, and more cavities were found in the lungs of the killed rabbits with reinfection experimental tuberculosis than in the animals with primary tuberculosis.

The author concluded that the study demonstrated a striking similarity between primary and reinfection types of tuberculosis produced experimentally in animals by a measured dose of organisms and the same types of tuberculosis as they occur in human beings.

Another approach to the acquisition of further information concerning the pathogenesis of tuberculosis is advanced by Sweany,<sup>20, 21</sup> who has made an extensive study of tuberculous calcifications. According to this author, primary calcifications can be differentiated from reinfection calcifications by the fact that, in general, the former are more heavily encapsulated and show a much greater tendency to ossification. Moreover, transitions from one type to the other occur with the development of allergy.

As a result of a study of multiple calcifications selected from over 600 autopsies, Sweany<sup>21</sup> concludes that "calcifications may result from any type of encapsulated tuberculous focus; namely, multiple primary seedings, scattered foci occurring in a resolving benign type of tuberculous pneumonia, in a hematogenous seeding occurring in the acute allergic period of the secondary stage of the primary, in various transition types from the primary into reinfection, in hematogenous reinfection, and in the healing of any form of tuberculous nodule or infiltrate arising from bronchogenic spread.

"By correlating the history, antemortem and postmortem roentgenographic findings, and the pathologic changes in multiple calcified lesions, it is possible in many cases to determine not only the character of the lesions themselves, but also attain an idea of the mechanism of the process leading up to their formation."

Frequent reference has been made in the literature to the report published by Heimbeck<sup>22</sup> in 1928 that clinical pulmonary tuberculosis developed much more frequently among nurses who entered training

on a tuberculosis ward in Oslo with a negative reaction to tuberculin, than occurred among those whose test was positive. This was interpreted as indicating that the nurses with the positive reactions were, as a group, more immune to tuberculosis than the negative group. Also, it is, or rather was until recently, the general impression that the acquisition of a tuberculous infection for the first time in adult life was likely to result in a severe form unusually resistant to treatment.

Myers' observations<sup>23</sup> on the development of tuberculosis among students of nursing and of medicine in the city of Minneapolis is of particular interest, therefore, in the bearing it has on these views. The students were tested to tuberculin upon entrance to the school and were usually retested at intervals of not greater than six months, since positive reactions known to have developed in such a short time possess diagnostic value in differentiating first infection lesions from reinfections which appear in x-ray films. When the interval between testing is a year or longer, this significance of positive tests is lost. Both the students of nursing and of medicine had opportunities for exposure to open cases of tuberculosis in their routine hospital work, and not infrequently the time and source of contagion could be ascertained quite accurately.

The individuals comprising the study are divided into six groups, on the basis of tuberculin reactions, and the type of lesions subsequently developed. Protocols are given for each patient.

Group 1 consists of two persons whose tuberculin reactions changed from negative to positive under observation and in whom erythema nodosum appeared.

In Group 2 are placed twenty-one persons whose tuberculin reaction changed from negative to positive and who developed a primary focus demonstrable by x-ray film examination. No other lesion was demonstrated. This is a significant group. They are adults never before infected with tuberculosis, but when they did become infected the resultant lesions were observed to run the same benign course as similar lesions which develop in infants and children. Over a period of time resolution went on to complete disappearance of the x-ray shadow or was reduced to fibrous strands or lime deposits. Symptoms were absent in the majority of these cases, and healing occurred without the employment of any special therapeutic measures. There was nothing characteristic about the x-ray shadows observed in these patients which served to differentiate between first and reinfection types of tuberculosis. (Compare with Burke's statement in experimental tuberculosis.) "It is only when one has carefully administered and interpreted tuberculin tests with sufficient frequency or has observed the lesions sufficiently long that such differentiation is possible," says Myers.

Group 3 is made up of nineteen cases whose tuberculin reaction changed from negative to positive and in whom primary parenchymal lesions were demonstrable by x-ray in some, and nondemonstrable in others. Pleural effusion also developed. This complication is looked upon by the author as a reinfection form of tuberculosis. The primary lesion sensitizes the tissues, and bacilli are transmitted to the visceral lymph channels from the lesion which frequently lies close to

the surface of the lung. While pleurisy with effusion occurs occasionally in infants and children who have acquired a recent first infection,

it apparently is more common in young adults.

Group 4 consists of twenty-five individuals whose tuberculin reaction changed from negative to positive and in whom clinical pulmonary tuberculosis later made its appearance, with or without demonstrable primary focus or pleurisy with effusion. Three of these patients have died from tuberculosis. In each of them the evolutionary course of the disease was followed from exposure to tuberculous patients to death with resultant lesions. The other patients have been treated by modern methods, and most of them have their lesions at least temporarily under control.

This is the group which, according to views once popular, should have developed severe and rapidly fatal tuberculosis. "However," states Myers, "their lesions are no more severe and respond just as well to treatment as the lesions which develop in adult life among per-

sons who were infected in infancy or childhood."

In Group 5 are included 15 individuals whose tuberculin reactions were positive when observation began, but in whom no evidence of clinical tuberculosis could be demonstrated. Later reinfection forms of tuberculosis made their appearance. In this group, then, a positive tuberculin test, indicative of previous tuberculous infection, did not produce sufficient immunity to prevent the development of clinical tuberculosis when exposure to tuberculous patients occurred. "Moreover," says Myers, "as far as we have been able to observe, the lesions which this group developed have not differed in intensity or in response to treatment from those who developed clinical disease after having become positive to the tuberculin test while under our observation."

Group 6 consists of four persons who had had no previous tuberculin tests, but negative x-ray films. All of them later developed extensive pulmonary tuberculosis. These patients are included in answer to the statement sometimes made that during the teen-age period x-ray films of the chest will reveal evidence of any disease which may cause illness at a later time in life.

Among the conclusions which may justifiably be drawn from this excellent piece of work are:

- 1. First infection type of tuberculosis possesses the same benign characteristics whether it occurs in infancy and childhood or in adult life.
- 2. The evolutionary course of tuberculosis is the same whether the first infection takes place in childhood or is delayed to adult life. A certain number will be followed by reinfection types of tuberculosis in either event.
- 3. The differentiation of pulmonary first infection and reinfection types of tuberculosis in adults depends upon one's knowledge of how recently sensitivity to tuberculin was acquired or upon long-continued x-ray study of lesions, unless symptoms characteristic of the reinfection form make their appearance.
- 4. Chronic pulmonary tuberculosis acquired by adults who have not been infected in childhood is no more severe or less resistant to treatment than is pulmonary tuberculosis which develops in adult individuals who have had positive tuberculin tests since childhood.

In the above paragraphs the attempt has been made to present a concept of the evolutionary course of tuberculosis from its earliest beginning when leucocytes phagocytose tubercle bacilli in the capillaries to the development of the chronic reinfection form of tuberculosis and to include the essential evidence upon which such a concept is based. There remains now the necessity of recording some of the published opinions of those who hold other views.

First of all, attention may be directed to the recently expressed opinions of Wallgren.24 of Gothenburg, Sweden, an author who has had an extensive experience with tuberculosis. Concerning the much debated question as to whether a first or primary infection equips the host with sufficient specific immunity to prevent the subsequent development of pulmonary tuberculosis, he advances the interesting theory that there are, or can be, two distinct types of immunity: one against exogenous reinfections and the other against the infection which is already in the body and which has produced pathologic changes. An analogous situation is found in syphilis, in which the syphilitic individual is immune against reinfection, but, nevertheless, if untreated, may die as the result of progressive activity of his original infection. The immunity to exogenous reinfections in tuberculosis, however, is only relative, but sufficient under ordinary conditions to protect a tuberculin-positive child from appreciable risk, if the child is subjected to new possibilities of infection. Under unfavorable conditions this relative immunity may be broken through, and reinfection may take place. But against the virus of the primary infection and development of disease from its foci, there is no noteworthy specific immunity.

Another significant point raised by Wallgren has to do with the definition of the term "reinfection." It is incorrect, he believes, and has led to much confusion, to speak of reinfection tuberculosis as including dissemination of bacilli from primary foci in the postallergic period. He would abandon the term "endogenous reinfection" and would restrict the meaning of reinfection to apply only to exogenous, or new infections from without.

To the question, "Is it advantageous to have passed through a primary infection?" he answers, "Yes and no." Were it possible throughout life to avoid with certainty the risk of virulent infection, then naturally, this would be best, for in this way could be avoided all tuberculous disease, including consumption. But obviously at present this ideal is not attainable, at least for the average city resident. It is, therefore, necessary to weigh the advantages of a first infection in childhood against its disadvantages.

The outstanding advantage of a successfully undergone primary infection is the relative specific immunity secured against exogenous reinfection pulmonary tuberculosis. But in the acquiring of the primary infection and for several months immediately following, particularly for young children, there is created a serious risk with reference to inception of tuberculous meningitis, miliary tuberculosis, pleuritis, and tuberculous peritonitis, all of which conditions are directly related to the primary infection. "Therefore," says Wallgren, "no one would in cold blood expose a previously noninfected child to a virulent tuberculous infection merely to let the child benefit later from the specific relative immunity which the primary infection creates.

The risks are too great. For this purpose there is, on the other hand, no risk in using Calmette vaccine, although the immunizing effect of this can possibly never be thought to compare with that of the virulent primary infection." But the child who is safely past the risk period must be considered to be in a more advantageous position from this standpoint than the child who has just been infected or who has not been infected at all. The point is illustrated by comparing a group of tuberculin-positive children with a group who are tuberculinnegative, all exposed to a consumptive teacher in a classroom. Nothing happens to the tuberculin-positive group, but some of the tuberculin-negative group will become ill, and one or more may succumb to meningitis or miliary disease.

If it be granted that the tuberculin-positive child has a degree of specific immunity toward exogenous reinfection and that he is past the risk period of meningitis, miliary disease, etc., there is yet a disadvantage arising out of the primary infection which merits serious consideration. In Wallgren's conception of the genesis of lung tuberculosis, he postulates the hematogenous dissemination of tubercle bacilli to various organs in the body very early in the course of the primary infection. Thus foci may be set up in the bones, joints, kidneys, peritoneum, pleura, and in the lungs at a point apart from the primary focus itself. Such foci create little or no tissue reaction, and they may remain in a state of latency until some special set of circumstances causes their activation. Tuberculosis of the bones and joints is generally understood to originate in this manner. And it is Wallgren's contention that pulmonary tuberculosis, or phthisis, not occasionally, but usually, is brought about in the same way. He says, "Tuberculosis of the lungs according to this concept is usually not the immediate result of introduction of tubercle bacilli either from the outside or the inside into the allergic portion of the lung, but is rather the effect of activity by tubercle bacilli, which in most cases of lung tuberculosis have long remained in the same place, but have not been able to start a progressive process on account of resistance on the part of the organism and especially the lungs."

Finally, he discusses the problem of why only 1 or 2 per cent of the general population develop pulmonary tuberculosis, and why it does not commonly make its appearance until the age of puberty has been reached. Neither variations in virulency nor dosage of organisms are responsible. Therefore, it must be due to variations in resistance in the infected organism and especially in the infected tissue that make it possible for some individuals to contract lung tuberculosis while others do not. The well-known fact that phthisis seldom occurs in children before the age of puberty suggests that allergy cannot be the sole factor responsible for the bringing about of lung tuberculosis, for the chances are that children who have been infected at an early age and thus have become allergic meet with reinfection as often as individuals in and above the age of puberty. That puberty shall have been reached, then, seems to be one of the essential requirements, and this in turn is probably intimately related to internal secretions. most significant factor, according to Wallgren, however, in order that lung tuberculosis shall develop from a primary infection, is probably hereditary disposition. Resistance-reducing factors such as unhygienic living, infections, and diseases, are important, but are secondary. "The first prerequisite that a lung tuberculosis shall develop is a tuberculous infection and this regardless of whether the infection occurs during childhood or later. The second prerequisite that lung tuberculosis shall develop is a disposition, and among all the constitutional and conditional factors, which together constitute the concept of disposition to consumption, the most significant are heredity and that the age of puberty shall have been reached," states Wallgren.

Opie<sup>25</sup> expresses still a different conception of the pathogenesis of tuberculosis from either that of Wallgren or of the Lymanhurst group. He regards first infection as a progressive disease, starting with an area of tuberculous pneumonia somewhere in the lung, progressing to adjacent lymph nodes, disseminating of tubercle bacilli by way of the blood stream to distant organs, as the spleen, liver, and meninges, and leading in many instances to death from generalized miliary tuberculosis. All of these ramifications are part of, and characteristic of, the first infection. In infancy it is accompanied by a relatively high mortality rate, but is usually benign throughout childhood. Adult negroes often exhibit the essential features of first infection tuberculosis as it is seen in white infants.

The type of tuberculosis which develops in adolescence and adult life is entirely different from the first infection type and is not, in his opinion, a continuation of the first infection, but is a new exogenous reinfection. However, its localization in the lung and its chronicity are referable to the immunity conferred by the first infection. Anatomic studies have repeatedly shown that at the time when the infection of adult life is progressive, the lesion of first infection is encapsulated and healed and there is no evidence that the former spreads from the latter. In a comprehensive study of the spread of tuberculosis in a thousand families Opie<sup>26</sup> and his associates have shown that in white persons first exposed to tuberculosis after fifteen years of age, pulmonary tuberculosis with few exceptions has the characteristics of the adult or reinfection type of the disease. marked increase in mortality rate over that of the general population occurring in persons over fifteen years of age exposed to open cases of tuberculosis is further evidence of its exogenous origin. more, recent roentgenographic study of married couples has given proof of the transfer of tuberculosis of the lungs from one to the other partner in nearly half the cases. Since this is a far greater rate than occurs in the general population, it can only be interpreted as indicating exogenous infection. Also, it was apparent in the study referred to above, that the severity of the disease in adolescents and adults as well as in children, varied, being more severe in the individuals exposed to open cases of tuberculosis than in those exposed to tuberculosis in which no dissemination of tubercle bacilli was demonstrable. Such variation is explainable on the basis of variation in the number of tubercle bacilli in the environment, which again shows that pulmonary tuberculosis is an exogenous infection.

It is apparent, therefore, that no unanimity of opinion concerning the pathogenesis of tuberculosis exists even among competent observers of wide experience. The lesions of first infection to one (Opie) become a closed chapter and, except for the immunity produced, bear no relation to the development of phthisis in adolescent and adult life. Phthisis results only from an exogenous infection, and only in

those individuals in whom the massiveness of the infecting dose overcomes the immunity imparted by the first infection. To another (Wallgren) phthisis seldom if ever results from an exogenous infection. The immunity set up by the first infection prevents outside reinfection. Phthisis results from an activation of tubercle bacilli planted in the lung usually years before, when hematogenous dissemination of organisms from the primary focus took place. In a third interpretation (Lymanhurst) phthisis may be the result of either an endogenous or an exogenous reinfection. For its development it is essential that there has been a preexisting first infection which has sensitized the tissues to tuberculoprotein. The immunity feature of the first infection is negligible.

No conclusions as to which of these concepts expresses the true situation is possible. The literature of the past year contains many excellent discussions bearing upon this interesting phase of tuberculosis which have not been recorded here because of space limitation. those interested, however, reference may be made to articles by Miller and Rappaport,27 by Pinner,28 and by Long 29

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# American Academy of Pediatrics

## Proceedings

# SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, Mo., MAY 11 AND 12, 1936

#### Round Table Discussion on Recent Advances in Nutrition

Chairman: Dr. W. McKim Marriott, St. Louis.

Assistants: Dr. Samuel W. Clausen, Rochester, N. Y.

Dr. Philip C. Jeans, Iowa City, Iowa.

CHAIRMAN MARRIOTT.—The aim of the nutritionist is to provide in utilizable form those materials which are necessary for the building up and maintenance of a bodily structure which will be functionally adequate. This aim may, to a considerable extent, be frustrated by such factors as heredity, congenital anomalies, or disease.

As the pediatrician deals with the body during the growing period, he may be compared with the builder of edifices; the internist and the surgeon, with the repair men. Given a solidly constructed structure, it will last well, and the minimum of repair work will be required. We cannot alter the general plans of the architect, but we can see that the proper materials go into the construction. Two buildings of the same size and outward appearance may differ greatly, depending upon the care taken in construction; the one may approach perfection in structure and wear well, the other, because of the use of poor materials, will not withstand wear and tear. It is so with the child's body; the architectural plan of nature may be excellent, but with skimping on materials a poor structure may result.

Adequate nutrition implies far more than the attainment and maintenance of a certain body size and weight or a certain thickness of adipose tissue. A child may be of average stature for the age and have an average height-weight ratio, yet the nutrition cannot be considered as satisfactory if the child is anemic, has weak flabby musculature, poor posture, hypoplastic or carious teeth, or a colloid goiter, or if he suffers from atonic constipation or night blindness, has but little resistance to infection, and is incapable of sustained physical or mental effort.

The growing body must be supplied with the necessary building materials to perfect its structure and to provide adequately for functional activity. If the total fuel or caloric value of the food is inadequate to provide for the energy exchange, the laying down of body tissues is of necessity interfered with, or else tissues already formed are destroyed to meet the energy demands. On the other hand, with an entirely sufficient caloric intake but insufficient protein and mineral salts, muscle, blood, and bone development may fail to keep pace with weight gain. Without sufficient mineral salts, protein cannot be laid down as active protoplasmic tissue. When vitamin D is lacking, calcium and phosphorus may not be deposited as normal bone structure even though these elements are supplied in liberal amounts. When the diet is deficient in carbohydrate, the processes of metabolism are deranged with the ac-

cumulation of potentially harmful ketone hodies. Even an abundant intake of all known dictary essentials may not result in normal nutrition unless a certain balance is preserved. Thus with what would ordinarily be an adequate calcium supply, a great excess of phosphorus in the dict may interfere with the utilization of calcium, and a great excess of calcium may interfere with the utilization of iron, and vice versa.

Even after normal body structures have been formed, these may sufter functional impurment due to lack of certain essentials in the diet. For example, epithelial structures become keratinized and readily invaded by bacteria when vitamin A is deficient; the gastrointestinal tract becomes atonic and the appetite is lost when vitamin B is deficient.

The digestibility of the food must of course be considered, especially in the ease of infants. In dealing with children, psychic factors must necessarily be taken into consideration. A balanced diet which may be relished by the laboratory rat may be refused by the child.

It is often stated that the instanct serves as a fairly reliable guide in the selection of foods, and examples are cited of primitive peoples with no knowledge of nutrition who instinctively choose well balanced diets and even of young children who, given free selection, choose diets which meet their nutritional requirements. While, in general, the instanct may lead the individual to select a complete diet, this cannot always be relied upon. All primitive peoples are not well nourished, and, unless a very wide choice of foods is readily available, certain essentials may be omitted, and the diet as a whole may be poorly balanced.

The appetite serves, in general, as a good guide to the total amount of food needed, and, provided a suitable dietary mixture is offered, there is but little danger of under or overfeeding when the amount of food taken is regulated by the appetite of a normal infant or child A child who has been underfed for a time will often take large amounts of food when given a free choice and gain at an extraordinary rate, but, as the nutrition improves and the weight approaches the norm for the age and the body build, the appetite falls off and the rate of gain becomes less. Normal infants and children, given all they wish to ext of a well balanced diet, are not likely to become evernourished. It is true that infants fed on the more modern concentrated formulas and given about all that their appetites demand are, as a group, larger and heavier than the accepted averages. They are not excessively fat. The fact that they are larger and heavier and have retained more calcium, phosphorus and nitrogen is not to be interpreted as meaning that they are oversized or over Such infants may be considered as approaching ideal body standards, which from the very nature of the case differ from average standards. It should be the aim of the pediatrician to have the child's nutrition approach the ideal rather than to keep it to the average.

It has been customary to consider the breast fed infant as the ideal and breast milk as the only perfect food; yet all breast milk is not perfect; nor do all mothers have a sufficient amount for their offspring. Breast milk is subject to greater daily variations then mixed herd cow's milk. There may be alterations in the total amount and in the calcium, fat, and vitamin contents, depending upon the mother's diet and living conditions. Breast milk, although adequate for the normal infant, does not contain sufficient protein for the special requirements of the premature or undernourished infant. Infants who nurse at the breast are likely to take considerably larger volumes of food than those offered carefully measured amounts of a formula from a bottle and hence they grow more rapidly. Given a good cow's milk formula under sanitary conditions, the ultimate results may, by all standards, be as satisfactory as those obtained with breast feeding

Certain individual constituents of the diet require special consideration. In the case of the infint and the growing child, there is an especially high requirement for

protein because of the laying down of new body tissue. The breast-fed infant receives about 10 per cent of the total calories in the form of protein, or approximately 2 gm. per kilogram of body weight. In the case of the infant receiving cow's milk, however, a larger amount of protein is needed because of its poorer nutritional value. A suitable allowance is 15 per cent of the total calories, or 3.5 gm. per kilogram of body weight per day. This corresponds to 1.5 oz. of cow's milk per pound of body weight per day. Infants receiving protein at higher levels grow somewhat more rapidly and have more solid tissues. A protein intake somewhat in excess of the average amounts mentioned above does little or no harm. The idea that moderately high protein feeding damages the kidneys of the human has failed of substantiation. A high protein diet does cause some hypertrophy of the kidneys but no pathologic changes. An insufficient amount of protein, on the other hand, results in slow growth and anemia. When the protein of the diet is low, the serum proteins are diminished in amount, and when, as the result of this, the colloidal osmotic pressure of the plasma falls below a certain level, nutritional edema of a greater or lesser degree occurs. As judged from clinical evidence, a low serum protein level is associated with decreased resistance to infection, possibly as the result of a lowering of the globulin fraction. Although animal proteins may more quantitatively be converted into body protein, satisfactory nutrition may be maintained through a proper selection of vegetable proteins; excellent results have been accomplished with the proteins of soy beans and of almonds. Some idea of the protein needs of the individual may be gained by consideration of the creatinine output. This phase of the subject will be discussed subsequently by Dr. Jeans.

The particular physical property of milk casein in forming curds during the processes of digestion has claimed a great deal of attention. One of the chief disadvantages of cow's milk for the feeding of the infant has been assumed to be the character of the casein, in that it forms large curds in the stomach. This particular disadvantage may be so easily obviated by heat treatment, acidification, or by other methods that it need not give us serious concern.

Fat is not as essential in the dietary as protein. Certain unsaturated fatty acids. such as linoleic acid, appear to be necessary for normal nutrition, but the amounts required are minimal. Linoleic acid may be considered in about the same category as the vitamins. Most natural fats carry small but adequate amounts of this fraction. The two important vitamins A and D are associated with the fats in natural foods. It is for these reasons that diets very low in fat are likely to be unsatisfactory unless especially supplemented so as to provide the essentials mentioned. In the average dietary about 35 per cent of the calories may to advantage be supplied by fat, but great variations in this amount may be made without noticeable effect on the nutrition. The most comprehensive study of the metabolism of fat, especially in infants, has been made by L. Emmett Holt, Jr., and associates.1 They have shown that the size of the globules in milk has little or no influence on digestibility and that digestibility is more related to the structure of the fat than to its melting point. Special fat mixtures designed to replace butter fat were shown to possess no particular advantages. An interesting reciprocal relationship between fats and mineral constituents of the diets was demonstrated, an excess of fat resulting in loss of certain minerals from the system and an excess of certain minerals leading to diminished fat utilization.

Carbohydrate is the most economical food both from the financial and metabolic standpoints. With self-selection of diets by older children and adults, approximately 50 per cent of the calories are ordinarily taken in the form of carbohydrate, and of this about one-half is starch and the remainder sugar. In the case of the young

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infant, sugars are the sole source of carbohydrate until starch is fed. When cow's milk is used for infant feeding, it has been empirically determined that a suitable amount of added carbohydrate is between 5 and 10 per cent of the amount of milk. Taking as an average 8 per cent, this will mean one half as many calories are added as carbohydrate as are furnished by the nulk. Too little earbohydrate necessitates excessive intake of fat and protein. Too much carbohydrate, on the other hand, may result in insufficient intake of protein. An additional disadvantage of high carbo hydrate feeding, particularly of sugar, is that of intestinal fermentation. Starch is more slowly digested and absorbed than sugar, hence does not flood the blood with glucose. As to the advantages and disadvantages of the individual sugars in infant feeding, experimental observations are conflicting. The normal infant appears to do about equally well when fed lactose, sucrose, or dextrin maltose mixtures. Sucrose leads to more rapid gain in weight than lactore and to more fat formation than the dextrin malto-e mixtures. Lactose is rather slowly absorbed and tends to change the butered flora of the large intestine to a type resembling that of the breast fed infant. There is some evidence that lactose feeding favors calcium absorption, possibly because of the formation of lactic acid in the lower portions of the intestinal tract. The mono-accharides, dextrose and levulose, are the most quickly absorbed of the sugars and require no digestive effort, they are, however, in concentrated solu tions, more irritating than the disaccharides and much more so than dextrin Dextrose and levulose are capable of absorption and utilization in patients with celiac disease who are unable to tolerate starch or the disaccharides

The mineral constituents of the diet assume especial importance during the growing period. Adequate amounts of sodium, potassium, magnesium, sulphur, and chlorine are likely to be contained in any average diet, and it is not usually necessary to make additions of these elements. Calcium, phosphorus, iron, and iodine may, on the other hand, be deficient unless the diets are especially selected or these elements added in inorganic form. Calcium and phosphorus seem to be better absorbed when given in the form of milk than in any other form, but, in general, minerals may be as satisfactorily supplied as simple inorganic salts as in specially selected diets. There would appear to be very little reason for taking large amounts of foods containing a few milligrams of iron or iodine per pound when simple in organic salts will supply every need. When cod liver oil is given to infants and children, a fair amount of iodine is supplied at the same time. Only a few natural foods contain significant amounts of iron, and the much vaunted spinach may when fed actually rob the body of iron. The metabolism of iron, of calcium, and of phosphorus will be discussed further in this symposium by Di. Jeans

The importance of the selection of foods providing an alkaline ash has been overrated. A diet having an ash approximating neutrality is perhaps the best, but a moderate variation on either the acid or alkaline side is practically without effect. Pollowing severe diarrhea or vomiting, the acid base balance may be greatly altered, and the same is true in the presence of diabetes or nephritis, but this does not concern us in considering the nutrition of the normal child.

Recent advances in our knowledge of the vitamins will be discussed by Dr Jeans and Dr. Chausen and thus will not be referred to at this time.

The state of nutrition may be influenced not only by the diet but by intrinsic body factors, such as heredity and the interrelationship of the various endocrine hormones, especially insulin, epinephrine, thyroxin, and numerous pituitary hormones \ detailed consideration of these would be beyond the scope of the present discussion.

It is not to be assumed that all factors influencing nutrition are as yet known Certain foods, especially fruits, seem to have somewhat specific effects which it is difficult to explain on the basis of what we know of the individual factors present. The severe digestive and nutritional disturbance known as celiac disease is still obscure so far as etiologic factors are concerned, yet it may be controlled by dietary means.

The discussion as related to certain specific factors in nutrition will be continued by Dr. Jeans.

#### Specific Factors in Nutrition

#### Philip C. Jeans, M.D., Iowa City, Iowa

NITROGEN METABOLISM AND MUSCLE GROWTH

At the time of birth and throughout the first year of life muscle tissue, according to Scammon, comprises approximately 25 per cent of the total body mass; at twelve years of age and thereafter the proportion is 40 per cent. Thus the muscle tissue undergoes not only an absolute, but also a relative, increase in relation to the remainder of the body. The time at which the relative increase occurs has not been determined.

It has long been known that creatinine exerction is proportionate to muscle mass. A study of creatinine exerction at various age levels should give information concerning the age period at which the relative increase in muscle mass occurs. It has been found that the creatinine exerction of the breast-fed baby is approximately 10 mg. per kilogram and that of the artificially fed baby who is receiving an abundance of food is 12 to 13 mg. per kilogram. The level of creatinine exerction per kilogram for the adult is approximately the same as that for the child of twelve years, viz., 20 mg. per kilogram. When the creatinine exerction per kilogram is determined at various age levels, it is found that the values remain practically constant until the age of three years. At approximately three years of age the values rise rapidly. This rapid rise continues until about nine years. After nine years of age the curve of increase becomes much less steep and before twelve years of age reaches the maximum level which is maintained thereafter. From these observations it may be concluded that the period of most rapid muscle increase in relation to the body mass occurs between three and nine years of age.

In the first year of life the relative amounts of creatinine excreted indicate that the artificially fed baby who is receiving ample food has a more rapid muscle growth than the breast-fed baby. The proportion of muscle weight to total body weight, though greater than that of the breast-fed baby, is maintained at a constant ratio throughout infancy.

This discussion has considered only the changes in muscle mass in relation to its proportion of the total mass of the body. Total growth is rapid in infancy and slows very definitely before three years of age, when the changed relationship between muscle and the remainder of the body begins. The absolute increases in muscle tissue are reflected in the nitrogen retentions. During the period of rapid growth in the first year, approximately 27 per cent of the ingested nitrogen is retained. From the age of one to three years, with the same nitrogen intake, the retention is only one-third of this value, representing a definite slowing in the speed of total growth, while at the same time the muscle mass remains the same proportion of the total body weight. Between four and nine years, while the muscle mass is increasing out of proportion to the total body weight, from 14 to 15 per cent of the ingested nitrogen is retained, even though the rate of total growth is less than it is between one and three years. After nine years of age the percentage of nitrogen retained Thus the nitrogen retentions offer further evidence that the again decreases. period of greatest relative increase in muscle is between three and nine years of age.

Many physicians are disturbed over the apparent loss of appetite between one and three years of age. Regardless of intake, children at this age retain less calcium, phosphorus, and nitrogen than at any other age period from birth to twelve years. From these facts it may be interpreted that the lessened food intake is physiologic and is not to be considered abnormal. The evidence seems equally clear that children from three to nine years of age need a high protein diet as much as do those in the period of adolescence.

#### EFFECT OF SUGARS ON CALCIUM AND PHOSPHORUS UTILIZATION

Animal experiments have indicated that conditions in the intestinal tract are much more favorable for the absorption of calcium and phosphorus when the food contains lactose than when it contains other sugars commonly used in infant feeding. On the basis of these experimental results many have assumed that in the artificial feeding of infants lactose would have the same favorable influence. The animal experiments were conducted with a relatively low intake of calcium and phosphorus, whereas the observations on infants have been made with a relatively high intake of these substances. The formulas consisted of undiluted milk with 6 per cent added sugar. With calcium and phosphorus retentions used as the criterion, no difference could be detected between the results with lactose and those with dextrin-maltose preparations. The same calcium retentions were observed with corn syrup as with the dry dextrin-maltose preparations. However, when dextrose was the added sugar in the formulas for infants under five months of age, the retentions were slightly but significantly lower than with the other sugars mentioned.

From a group of infants from eight to thirteen months of age whose retentions had been under continuous observation previously, those were chosen who had the lowest retention values. For this group of selected infants lactose was substituted in the formula for the dextrin-maltose mixture previously used. In the thirteen studies made, no increase in retentions was observed as a result of the substitution. It is possible that some difference might have been found had the amount of milk been less or the amount of added sugar greater, but the proportions used were those commonly employed in infant feeding.

From these observations it may be concluded that no significant difference is to be observed in calcium retentions when comparison is made between feeding formulas containing lactose and those containing dextrin-maltose mixtures when the formula consists of undiluted milk with 6 per cent added sugar. Under these same conditions the use of dextrose as the added sugar apparently permits significantly smaller calcium retentions than those obtained with the other sugars mentioned.

#### DEXTROSE IN MALNUTRITION

In the condition known as celiac disease, a diet high in protein and in monosaccharides and low in fats and complex carbohydrates has proved uniformly successful. Since one of the prominent symptoms of children with celiac disease is malnutrition, it seemed possible that children with malnutrition from other causes might benefit from this same type of diet. When this idea was put to the test of trial, it was found that malnourished children utilize the celiac type of diet far more efficiently than either the average normal diet or one high in fat.

Children who were markedly underweight did not make consistently good gains on the average diet until the energy intake reached 50 calories per pound. At this level fair gains were made also with a diet high in fat, but these were not as satisfactory as those with the average diet. However, when the celiac type of diet was administered at the level of 50 calories per pound, the gains were very rapid, some children increasing their weight at the rate of a pound a day for considerable periods.

When the energy intake was maintained at approximately 35 calories per pound, children receiving the celiac type of diet made fair gains, whereas with the average diet and the high fat diet at this level no gain was observed. When malnourished children are receiving a high fat diet in sufficient quantity to permit gain in weight, a greater gain in weight will be observed if the energy intake is reduced by 500 calories and the celiac diet substituted for the high fat diet.

Certain fruits are relatively rich in monosaccharides. Equivalent amounts of these fruits may be substituted for dextrose in the celiac diet, and the results are the same. Substitution of bananas in this manner gave results identical with those de-

scribed for dextrose. In the celiac, or high dextrose, diet the amounts of dextrose varied from 250 gm. daily for a child of six or seven years to 500 gm. for a child of twelve or thirteen years.

It might be assumed that weight gains made as a result of a high sugar diet would consist largely of water. It is possible that this is true for the rapid gain of the first few days of the diet. However, metabolic observations have demonstrated conclusively that the net result is a substantial increase in useful tissue rather than water. This was indicated by the high retentions of mitrogen, calcium, and phosphorus and by the increased excretion of creatinine. It was observed that when the weight increased 20 per cent, the creatinine excretion increased 35 to 40 per cent.

These observations demonstrate that the malnourished child utilizes a high dextrose, low fat diet much better than the average normal diet and far better than a high fat diet. The same is true to a far greater degree with a child with celiac disease. It seems entirely possible that malnutrition itself may be an important determining factor in the production of celiac disease.

Malnourished children practically always are ingesting a diet which provides considerably less energy than the requirement. It is entirely logical to think of such a child in terms of a greater food intake. It may be logical also to think of cream and other fats as providing the additional energy in small bulk. With great frequency one finds that dietary increases have been advised along these lines. The observations of the preceding discussion demonstrate the fallacy of this type of advice. Much greater success will be attained with the high dextrose diet and at a lower energy intake.

#### IRON

The infant at the time of birth has a small store of iron. The amount varies greatly but does not average more than approximately 15 mg. or an amount which would be necessary for the formation of about 50 c.c. of blood. For approximately two months after birth a rapid destruction of hemoglobin occurs. As a result, from 150 to 200 mg, of iron is liberated. It is the general concept that all of this iron is stored for use in hemoglobin formation and that this amount is sufficient to supply the iron needs of the infant until six months of age. On a theoretical basis it is true that if all of this iron were conserved, the supply would be just sufficient for the needs up to six months. However, about 30 per cent of the iron freed from hemoglobin during the first two months is lost. During the period of hemoglobin destruction all infants are in negative iron balance. The diet supplies approximately 0.75 mg. of iron daily and the excretion varies from 1.5 to a high value of 4 mg. daily, producing an average negative balance of 1.35 mg. of iron daily. The stored remainder, equivalent to 300 to 375 c.c. of blood, would be sufficient to supply the iron needs until the age of about 4.5 months only if it were well conserved. However, babies receiving the usual milk formulas without additional iron are in negative iron balance during this period, and the reserve supply is exhausted before the theoretically calculated age. On this basis it becomes obvious that the diet of the infant requires consideration as regards iron considerably before six months of age.

The amount of hemoglobin present during infancy is less than at a later time. It is the general custom to consider this condition as normal. When statistical surveys are made and averages determined, these averages do not necessarily represent the normal. The finding of dental caries in 80 per cent of all school children would not be considered normal merely because it is an average of existing conditions. Elvehjem has found that, by giving an abundance of iron-containing foods to a selected group of infants, the average hemoglobin was more than 1 mg. to 100 c.c. greater throughout infancy than usual average values.

In order to maintain an infant in iron equilibrium, it has been found that the daily ingestion of 0.5 mg. per kilogram in the form of readily available iron is

necessary. It has been calculated that an average retention of 0.75 mg. daily is necessary to maintain normal hemoglobin formation. In order to attain this amount of retention, an average intake of 0.7 mg. per kilogram is necessary. These statements apply at all ages from seven weeks to one year of age. A general impression that babies under six months of age do not use ingested irons seems to be erroneous. Intakes of iron greater than 0.7 mg. per kilogram lead to greater retentions up to an intake of approximately 1 mg. per kilogram, above which amount little or no increase in retention is to be observed. Ingestion of iron in excess of this amount not only is without benefit, but may be actually harmful. It has been shown quite definitely for the chick that the feeding of iron in amounts comparable to the high dosages recommended at times by physicians for severe anemia produces within 1 to 2 weeks severe low phosphorus rickets, with death of all the chicks within three weeks.

On the basis of the preceding discussion the iron requirement of the infant may be met satisfactorily by the ingestion of 5 mg. daily from three to six months of age and 10 mg. daily from six to twelve months. These amounts will permit an average retention of 0.75 mg. daily, an amount calculated to be necessary.

Cow's milk varies greatly in its iron content, depending on the method of handling. As the milk comes from the cow, it contains approximately 0.2 mg. per liter. With transport in tinned iron containers it may acquire a content of 2.5 mg. per liter. The average of values obtained by six different observers is 0.6 mg. per liter. The usual milk formula of the artificially fed baby, including the customary orange juice supplement, may be relied upon to supply approximately 1 mg. of iron daily. If no other source of iron is made available, the infant will have a definite and often a marked deficiency by six months of age.

It is the custom of many to add egg yolk to the diet at the fourth month or even earlier. An egg yolk contributes approximately 1 mg, of iron. This amount in addition to the formula would still leave a deficit, even if the iron of the egg were all utilized. Balance experiments have shown, however, that the iron balance when egg yolk is fed is little different from that of the same diet without egg. The reason for this is not clear, unless it may be accounted for by the sulphur content.

Vegetables have had an extensive usage in infant feeding. One of the functions is to supply iron. They are often added to the diet at a relatively early age. It is necessary to concede to vegetables a certain usefulness. However, in the case of spinach we seem to have a product of overestimated value. Canned puréed spinach ready for use contains approximately 0.35 mg. of iron to the ounce. With a large serving of spinach the amount of iron obtained by an infant would be from 0.5 to 1 mg. This amount of iron would not contribute greatly to the total requirement even if it were all utilized. Balance experiments have shown that not only is the iron of spinach not utilized, but the already negative balance of the infant is made greater. Presumably this effect is produced by the oxalate content. Spinach has the same effect on the calcium balance, probably for the same reason. Spinach seems to serve little useful purpose in supplying the mineral needs of the body, Popeye to the contrary notwithstanding.

The proprietary cereal food pablum contains 6.8 mg. of iron to the ounce of dry preparation. This is a higher proportion of iron than is found in any of the natural foods. Much of this iron is in the powdered alfalfa content. Balance experiments show that the iron of pablum is well utilized. The utilization is better than that with egg yolk and the same as that with ferric ammonium citrate.

It has long been recognized that iron ammonium citrate is well utilized. This material is not a definite crystalline substance, but varies somewhat in its iron content. One cubic centimeter of a 1 per cent solution contains 1.5 to 2 mg. of iron. In order to meet the iron requirement of the infant up to one year of age.

5 c.c. of a 1 per cent solution is ample. This supplies from 7.5 to 10 mg. of iron. More than this amount is unnecessary and amounts greatly in excess are likely to be definitely harmful. Though babies need more iron than most of them get, the overzealous administration of iron will do more harm than good.

#### VITAMIN D

Vitamin D as it occurs in nature or is produced by irradiation is of two varieties, one of animal origin related to cholesterol and the other of vegetable origin related to ergosterol. On a rat unit basis these two varieties have markedly unequal values for the chick and to a lesser degree for the human infant. The evidence may be interpreted to indicate that approximately 1.5 times as many rat units of vegetable source vitamin D are required as of animal source vitamin D to produce the same effects in the human.

The smallest amount of vitamin D recommended to the public as being adequate is the amount found in irradiated milk, which contains 135 U.S. P. units to the quart. This amount of vitamin D will prevent and ultimately cure rickets in most instances. It has been found also that cod liver oil concentrate dispersed in milk and cod liver oil separately have the same effects as irradiated milk when administered on an equal rat unit basis.

Rickets prevention has had almost universal acceptance as a criterion of adequacy of vitamin D. If this is an acceptable criterion, 60 to 135 units of animal source vitamin D constitutes an adequate amount, instead of the 1,000 units or more in the recommended dose of 3 teaspoonfuls of cod liver oil. The discrepancy between these two recommendations is more than 600 per cent.

Evidence has been produced to show that rickets prevention is not a criterion of sufficient vitamin D. Babies receiving irradiated milk or its equivalent do not grow as well as those receiving a larger amount of vitamin D. Balance experiments show significantly smaller retentions of calcium and phosphorus with irradiated milk than when the amount of vitamin D in 1 teaspoonful of cod liver oil is administered. If babies receiving irradiated milk have inferior growth and inadequate calcium retentions, this amount of vitamin D cannot be accepted as satisfactory.

The minimum amount of vitamin D which will permit satisfactory growth and calcium retentions has not been determined, but it has been shown that the amount in I teaspoonful of cod liver oil is ample and perhaps in excess of the minimum requirement. It is indicated also that amounts of cod liver oil greater than I teaspoonful will cause no further increase in growth or in calcium retention. Apparently the maximum beneficial effect is obtained with a I teaspoonful daily dose.

#### VITAMIN A

The general impression has obtained that vitamin A deficiency is infrequent in our general population. This opinion has been based on the relative infrequency of xerophthalmia and of night blindness. Apparently xerophthalmia depends on an extreme deficiency, and it is not surprising that this condition is uncommon. Because of the necessity for a marked deficiency in order to produce xerophthalmia, this condition could not be used as a criterion for lesser but significant degrees of vitamin A deficiency. Similarly, night blindness of sufficient degree to be a cause of complaint cannot be a good criterion. Conclusions based on questionnaire surveys concerning the frequency of night blindness must take into consideration the fact that routine ophthalmologic examinations do not detect night blindness. It is diagnosed usually only after complaint is made and special tests applied. It seems probable that significant degrees of night blindness of which the subject is aware are more common than is usually assumed. It is certain that moderate degrees of night blindness of which the subject may be unaware are exceedingly common.

When a special test for dark adaptation is applied, departures from the normal are found with considerable frequency. It is easily demonstrated that at least in the great majority of instances these abnormal results are dependent on vitamin A deficiency; when vitamin A is administered, the subjects develop normal dark adaptation. The great frequency with which vitamin A deficiency is found by this procedure would seem to demand attention. If anything like half of the children of this country are ingesting diets deficient in this respect, some kind of educational propaganda is indicated. It has been determined that a good diet containing ample vitamin A can easily be selected from common readily available foods. When such a diet is used, apparently vitamin A concentrates are not necessary. This fact being recognized, what should be the status of vitamin A concentrates? Should they be recommended for routine use or should their use be discouraged? Should vitamin A additions to foods be permitted?

Educational propaganda directed by nutritionists and physicians to the mass of people at large has had and for a long time may be expected to have only a very limited effect. Propaganda sufficiently extensive to be effective is economically impracticable, and to a considerable extent an urgent incentive is lacking. If we await optimistically the time when all of the people will select good diets because of this type of instruction, many will continue to have dietary deficiencies indefinitely.

On the other hand, if we accept and encourage the commercial exploitation of this need, a potent incentive with economic backing and considerable initiative immediately comes into the picture. Results will be more far-reaching and will be attained more quickly. If people persist in selecting foods containing little or no vitamin A, what possible harm can come from additions of this substance to certain of the most common foods selected for this purpose because of their appropriateness as a vehicle for vitamin A and because of their widespread use?

## Observations on the Anti-Infective Action of Vitamin A and on Moderate Deficiency of Vitamin C

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Within the past few years, exact knowledge of the chemical and physical properties of vitamins A, B<sub>1</sub>, C, and D has accumulated with breathless speed. Methods for quantitative chemical estimation of carotene, the precursor of vitamin A, for vitamin A and for vitamin C are now available, methods which surpass in delicacy, exactness, and speed the biologic methods. For these reasons, workers sometimes ignore the fact that the chemical and physical methods are specific for the substances in question only when certain criteria are met. If not, conclusions based upon the use of the newer technic will be fallacious. Under properly controlled conditions, however, clinical results otherwise unattainable must result. With the pure vitamins now available, we shall be able eventually to settle with certainty questions of specificity; to determine the actual requirements of these vitamins under various conditions of age, sex, and disease; to discover states of "subclinical" deficiency; and to ascertain the upper limits of safe dosage. Moreover, with pure vitamins, it is possible to avoid the untoward effects which may result from substances which accompany the vitamins in nature.

Our own work has been concerned with the analysis of fluids and tissues of the body for carotene, xanthophyll, vitamin A, and vitamin C. Two questions will be considered: (1) the anti-infective action of vitamin A, and (2) the application of the newer methods to the study of deficiency of vitamin C.

#### THE ANTI-INFECTIVE ACTION OF VITAMIN A

McCollum in 1917 first showed that rats with xerophthalmia were liable to spontaneous infections. This work has been confirmed and extended by many other workers. It has been shown that the spontaneous infections of the respiratory tract are

associated with the metaplasia of the respiratory epithelium characteristic of severe deficiency of vitamin A. The lowering of resistance to experimental infection with the paratyphoid group of organisms in rats may be due in part to metaplasia of epithelium; but, since the barriers of the liver, spleen, and bone marrow failed to prevent bacteremia in the feeding experiments of Lassen, it is evident that some factor other than epithelial metaplasia must be involved. In these experiments the infections were induced after the deficiency had fully developed. Bradford and Boynton, and later McClung and Winters, showed that rats receiving diets deficient in vitamin A became susceptible to infection before loss of weight or any other sign of deficiency developed. This suggests that mild forms of vitamin A deficiency may be a cause of susceptibility to infection. This suggestion receives support from the studies of Webster and Pritchett, who showed that mice raised for generations on a diet hitherto considered adequate were less resistant to inoculation with mousetyphoid bacilli than were other mice whose diet was supplemented by the addition of cod liver oil or butter. Topley, Greenwood, and Wilson were apparently unable to confirm this work, but in their experiments, the deficient diets were not begun until relatively late in the lives of the mice. In all the work so far mentioned, no analyses were made of the tissues for vitamin A. Some observations of McCoy and McCoord may serve to reconcile the different conclusions of the authors mentioned. In their work, rats of varying age were depleted of vitamin A, as shown by a negative Price-Carr test for vitamin A, and then infected with trichinosis. The young rats were invariably more susceptible than the controls which received supplements of halibut liver oil. The older rats-even though their livers were devoid of vitamin Awere only slightly more susceptible than the controls. More work must be done, using other infecting organisms, various portals of entry, and other hosts. The study of the effect of a deficiency in fetal life or in early infancy, followed by normal diet, would also be of great clinical significance. The experimental work may be summarized by the statements: Frank deficiency of vitamin A in most animals leads to increased susceptibility to spontaneous and to artificial infections. There is no evidence that animals with adequate stores of vitamin A may be rendered more resistant to infection by administering carotene or vitamin A, although there is some evidence that some of the standard diets in use may be so improved.

With this brief discussion of experimental results, we may now consider the evidence for the anti-infective action of vitamin A in man. Bloch in 1928 reported his very extensive observations of xerophthalmia in Denmark and called attention to the frequency of severe infection in his 109 patients. Later he stated his belief that the liability to infection persisted even after cure of xerophthalmia. A liability to infection in xerophthalmia is, however, not evident in the reports of Spense or of Blackfan and Wolbach. Efforts to lessen the incidence and severity of infections in infants without xerophthalmia by the administration of cod liver oil, concentrates of vitamin A, or carotene have on the whole been unsuccessful. Erben reports success; Barenberg and Lewis, and Hess, Lewis and Barenberg report complete failure. Helen McKay finds no increase in resistance to respiratory infections but reports a decrease in infections of the skin. We have noticed in the reports of the work of Hess and his colleagues that only 7 per cent of the infants were under the age of six months and that the diet in very early infancy was not described. Therefore, we have analyzed in our own cases the feeding histories from the age of two months. We find that the addition of cod liver oil to the diet by the age of two months confers no increase of resistance to infection during the first six months of life but that the addition of cod liver oil by the age of two months and the inclusion of vegetables after the age of five months appears to confer considerable resistance between the ages of six and twenty-four months. This effect disappears in large part after the age of two years. The criticism that the control cases may not be comparable with those receiving additions of vitamin A is difficult to meet, for these

cases are largely children of families who fulled to follow all kinds of advice. The results, however, suggest that the infant in early life may require very much larger amounts of vitamin A than in later life. Our own work confirms the findings of several other workers that the liver at birth, especially in the case of premature in fants, contains very little vitamin A and that colostrum is exceptionally rich in carotene and in vitamin A. We are at present studying the vitamin A requirements of the fetus. The blood of the umbilical vein always contains more carotene than does that of the umbilical artery, whereas the average concentrations of vitamin A in vein and artery are equal. A conservative, if not very accurate, estimate shows that at the time of birth, the fetus may be receiving 1000 international units of vitamin A as carotene per kilogram of weight each day. We are planning to study the effects of early administration of vitamin A upon subsequent tendency to infection in a carefully controlled series of eases

The influence of administering vitamin A to older children and adults upon re sistance to infection has been the subject of many conflicting reports and his coworkers in 1931 claimed that a preparation of vitamins A and D would lessen the incidence of postpartum fever and applied to vitamin A the unfortunate adjective "anti infective." The term "anti infective vitamin" has served to stim ulate the publication of much uncritical work. Holmes, Pigott, Sawyer, and Com stock administered one tablespoonful of cod liver oil a day to a volunteer group of industrial workers. The incident of common colds and the loss of time from work was less than in a group of "controls" who refused to take cod liver oil administered a concentrate containing vitamins A and D in 600 alternate cases of measles. Although the incidence of pneumonia and of otitis media was the same in both groups, the mortality was 3.7 per cent in the group receiving the vitamins and 87 per cent in the other. The fact that the two groups occupied separate wards renders the evidence less convincing. Recently several other authors have claimed that the administration of carotene lessened the incidence and severity of respiratory infections

Equally impressive evidence has been recorded that the administration of vitamin A during an infection does not lessen its severity. Suthfi, Place, and Segod administered 400,000 U. S. P. units of vitamin A per day to 509 children with searlet fever. The incidence of otitis media was 9.4 per cent. The expected incidence was 11.3 per cent. Alternate cases were not treated.

We have made a similar study, using carotene in scarlet fever, with no beneficial results. Studies of the blood showed that the carotene had been absorbed, although the level of blood carotene was less than that which was produced by the same dose in convalescent children.

For several years we have administered carotene in children living in foster homes in effort has been made to keep the experimental and control groups as nearly alike as possible. We have been unable to observe any lessening of the incidence of infection or any decrease in its severity in the treated children

Two chief criticisms can be directed against the clinical reports. (1) It is difficult to be certain that the experimental and the control groups are comparable, and (2) criteria have not been furnished that a deficiency of vitamin A existed in the subject. From a study of carotinoid pigments of the blood in a large group of children, together with clinical histories of susceptibility to colds, we have concluded that not more than 5 or 10 per cent of the children might have been benefited by the administration of carotene. It is obvious that if subjects for the administration of carotene are selected at random, any beneficial effects may not appear on statistical analysis. We need an extensive experiment in which children with habitually low blood carotene are selected for a controlled test. Analysis of the liver, which is the great storchouse of vitamin A, often shows a marked decrease in persons who have died of severe in fection. This decrease in vitamin A is not sufficient evidence that these persons

had suffered from a deficiency of vitamin A before the infection. We have found that the stores of vitamin A in the livers of rats are depleted by infection and that the degree of depletion depends upon the severity and the duration of the infection.

It may be concluded that the administration of carotene or of vitamin A cannot be expected to increase resistance to infection in older persons who are not suffering from deficiency of vitamin A. Sufficient studies have not been reported of the anti-infective value of vitamin A in persons who actually are deficient. On the other hand, there is evidence that the young and rapidly growing infant may require abundant vitamin A in order to develop resistance to infection in early life. The actual requirements of vitamin A for this purpose are not known.

#### TEST FOR DEFICIENCY OF VITAMIN C

In clinical conditions supposed to be due to deficiency of vitamin C, four diagnostic tests have been proposed:

- 1. The "Therapeutic Test."—The condition must be relieved by the administration of vitamin C. The therapeutic test may be carried out with pure cevitamic acid. A number of reports have appeared on the cure of scurvy and the relief of prescorbutic symptoms by this method. Some years ago, Theobald Smith observed that guinea pigs during the winter were subject to pneumonia, which tendency disappeared as soon as fresh fodder was available. These experiments have been extended by von Euler, who has been able to show that fresh vegetables and fruits contain the anti-infective agent even after the vitamin C in them has been destroyed. These experiments are mentioned in order to show that relief of symptoms with fruit juices may not be proof that these symptoms are due to deficiency of vitamin C.
- 2. The Capillary Resistance. Göthlin and his coworkers, using a standardized technic for the Leeds-Rumpel test, report decreased capillary resistance in persons consuming a diet low in vitamin C. Dalldorf, using measured negative pressure, reaches the same conclusion. Both investigators find that the administration of vitamin C increased capillary resistance. The reports of Greene and of Toverud fail to confirm the claims of these authors. Abt, Farmer, and Epstein find no relationship between the capillary resistance and the level of reduced cevitamic acid in the plasma. Hawley, Stephens, and Anderson, using a modification of the negative pressure method, observed no increase in capillary resistance in subjects after receiving large amounts of orange juice or of cebione (Merck). In these studies the daily output of cevitamic acid in the urine was measured. Hawley has observed one case of seurvy in which a marked and prompt increase in capillary resistance followed the oral administration of cebione and another, in which the capillary resistance was normal. She has also observed one case of thrombopenic purpura in which there was a close correlation of capillary resistance with the intake of vitamin C over a period of many months. In several other cases of purpura no such correlation was observed. Her observations seem to indicate that the discordant reports in the literature are not due to differences in technic or interpretation, but depend upon factors not understood. It is obvious that the tests of capillary resistance are not reliable indicators of vitamin C deficiency at the present time.
  - 3. Chemical Analysis of Urine for Vitamin C.—Under proper conditions, titration of urine with the indicator 2:6-dichlorphenolindophenol is an accurate measure of its content of vitamin C. The iodine titration, reliable for certain fruits and vegetables, gives high results with urine, mainly owing to the presence of sulphur compounds. Using the dye method, Harris and his colleagues have shown that the urinary output of vitamin C is an accurate measure of the intake of vitamin C. The claim of Beszonoff that infants under four months of age are able to synthesize vitamin C appears to be unfounded. Abt and his colleagues believe that the excre-

tion of vitamin C, observed by Beszonoff, is wholly explained by the slow elimination of the stored vitamin. Hawley is at present engaged in a study of the vitamin C content of human colostrum and milk. She has shown that an increase follows within an hour after the ingestion of orange juice. She is also observing the output of cevitamic acid in the urine of infants on various analyzed diets and finding a close correlation between intake and output. She finds no evidence that the young infant is able to synthesize its own vitamin C. We have observed that patients receiving diets for gastric ulcer are invariably undersaturated with vitamin C. nephritis the output of vitamin C is likely to be low. This is in part due to the rapid disappearance of vitamin C in the urine itself. The acid-base balance of this diet also affects the output of vitamin C when the intake is constant. Hawley and her coworkers have conducted an extensive experiment showing clearly that the measured output of vitamin C is reduced when the urine is alkaline. They have shown that the loss of vitamin, due to its destruction of oxidation in a medium as alkaline as the urine in question, does not wholly explain their results. An experiment involving the analysis of tissues of guinea pigs on various diets is in progress in the attempt to account for the findings. It is apparent that analysis of urine is an important and reliable method of investigation.

4. Analysis of Blood and Tissues.—The reports of Abt and his colleagues indicate that analysis of blood may become a satisfactory method for diagnosis of scurvy and prescorbutic conditions. Our own observations, few in number, fully confirm this opinion. Unpublished results of Clayton show that the tonsils contain abundant cevitamic acid and that the concentration depends upon the previous diet. She has observed a decrease in chronic infections but has not been able to show exceptionally low values in rheumatic fever.

#### CONCLUSIONS

The newer chemical and physical methods for quantitative estimation of vitamins A and C afford useful tools for the investigation of clinical problems. They will prove most fruitful as a supplement to accurate clinical observation.

#### GENERAL DISCUSSION

DR. JOHN ZAHORSKY (St. Louis).—I desire to bring up the question of overgrowth in infants. The high protein content of modern milk mixtures fortified by concentrated vitamin has a distinct tendency to product an overgrowth. It is very common now to obtain the same growth in the first year which we formerly believed required two years. Moreover, the fontanel is closed in so many of these infants at one year or less. The brain, however, does not quite keep pace with this somatic growth. The question whether this overgrowth during infancy is ultimately advantageous or detrimental to the child requires serious consideration. In animals the growing period to maturity can be shortened by heavy feeding. Are we going to shorten the period of childhood by this superalimentation?

In a study of 50 infants who were overgrown, we find a distinct tendency for the weight to approach the normal after the infant is eighteen months old. This makes it necessary that the child stop growing and, I believe, is the prime impulse in the nervous anorexia so common at this period. The administration of vitamins  $\Lambda$  and C regardless of the rate of growth seems entirely irrational. The child stops eating but he has to swallow viosterol. I am discouraging the routine use of the concentrated vitamin during the summer months and after the third year.

CHAIRMAN MARRIOTT.—Dr. Zahorsky is to be congratulated on the excellent nutritional results he obtained. The good nutritional results with generous feedings last to adult life.

The observations of Gray on boys in a private school showed that children of the better classes, well fed from the age of infancy, averaged distinctly larger than accepted normal standards. We know further that children today with better methods of nutrition are decidedly taller and heavier than the children of ten or fifteen years ago.

DR. JEANS.—Mental tests show higher ratings for babies who grow well. For several seasons it has been observed that babies kept on low vitamin D intake for experimental purposes did not do well. I think that 1 dram of cod liver oil is enough even under poor conditions if the food is good.

DR. JAMES A. WHEELER (NEWTON, KAN.).—Dr. Zahorsky stated that he wonders what will happen to the mental side of children by the newer feeding standards. I have been informed by several men who have worked in the child guidance centers that the problem is not strictly confined to the child but is mainly one with the parents. Most of these parents were fed under earlier methods.

DR. JOHN R. VONACHEN (Peoria, Ill.).—Since Dr. Marriott mentioned the possible relationship between a high protein intake and premature senility, it occurred to me that there might be some connection between this and progeria. I remember the case of progeria because of its unusualness in that this child had taken between two and three quarts of lactic acid milk up to the age of almost three years. I saw her when she was about twelve years of age, not because of the high lactic acid milk intake but for the progeria. This child was so fond of the lactic acid that she preferred it to other milks. I mention this because of its unusual occurrence rather than it had anything to do with the progeria. However, I would like to ask Dr. Marriott if there could be any possible relationship.

CHAIRMAN MARRIOTT .- I doubt if there could be any relationship.

DR. MAURICE L. BLATT (CHICAGO).—What is the advantage of excess weight with monosaccharides?

DR. JEANS.—The large gains reported were in children who were 20 to 30 per cent underweight. Gains can be made better with a high dextrose diet than with fat. The increased gain tended to cease when the child had attained normal weight.

DR. BLATT.—In considering the weight of a child, its chronologic age, its height, whether it was premature or full term, and its build have to be taken into consideration. Children usually resemble their ancestors in stature. It does not seem important that a child be given additional food for no other purpose than to put on weight. In my experience, thin children enjoy quite as good health and are quite as long lived as are fat ones. Lack of weight due to disease is, in my opinion, not well treated by feeding carbohydrate for the purpose of increasing weight. A gain in weight occurring in a child ill with an infection is usually an indication of the child's general improvement.

DR. ARTHUR F. ABT (CHICAGO).—What significance does Dr. Marriott attach to the relationship, stressed by L. F. Meyer of Berlin, between fat and carbohydrate which is a 1 to 2 ratio in breast milk? Meyer contends that the failure of every effort with straight cow's milk has been solely due to its 1:1 ratio. He further believes that fat restricts, while carbohydrate favors, water retention and that for the normal metabolism of the human infant the 1:2 ratio of fat to carbohydrate is necessary.

CHAIRMAN MARRIOTT.—Most infants do somewhat better when the proportion of carbohydrate exceeds that of fat, but that this is not necessarily the case

has been repeatedly demonstrated in the case of diabetic infants and children, in whom excellent nutrition has been maintained on high fat diets containing a minimum of carbohydrate.

DR. JAY I. DURAND (SEATTLE, WASH.) .- How much milk should a child take?

CHAIRMAN MARRIOTT.—I do not know. It depends upon the child. If one refers to the experiments of Dr. Clara Davis and the experience of children in the tropics, it is recognized that one gets good results with a varied diet.

DR. JEANS.—The criterion may be the calcium intake rather than other food. Milk is the chief source of calcium.

DR. EVON ROSENSTERN (Berlin, Germany).—At one time our children were getting a liter or more of milk. They were fat and had poor resistance. Lately we have given less milk, one-half liter, and more vegetables. The state of health on this schedule is better. The height of the population in Germany during the last fifty years has increased about 5 cm. In recent years the height of children was lessened. There were various theories as to the cause of that. It was thought to be due to lack of food after the war or due to rickets that many children developed before and after the war. We studied the growth of breast-fed and artificially fed babies and noted that the calcification centers developed earlier with artificial feeding.

DR. ZAHORSKY.—Does the incidence of rickets in infancy and early childhood have a tendency to produce shorter adults? I have a distinct impression that moderate rickets without deformity has no effect on the final height of the person. Or is this due to the fact that rickets occur generally in the infant who has a natural tendency to be tall?

CHAIRMAN MARRIOTT.—Many individuals who have had severe rickets during infancy and early childhood remain permanently dwarfed.

DR. JEANS.—I think that growth will be compensated later if the rickets was not too severe. I am not sure that the improvement in children referred to by Dr. Rosenstern is due to less milk or to other food given.

DR. B. FEINBERG (PROVIDENCE, R. I.).—I wonder whether Dr. Marriott has had any experience with small doses of thyroid in premature infants?

CHAIRMAN MARRIOTT.—We have not had any experience in the use of thyroid in normal premature infants.

DR. MARTHA M. ELIOT (New Haven, Conn.).—1. Dr. Jeans has indicated the efficacy of vitamin D in relation to growth. Does he think I tenspoon of cod liver oil will provide a sufficient margin of safety?

2. If 400 units are believed to be necessary for optimum calcium retention, should additional vitamin D be given to infants and children besides that contained in irradiated milk?

3. What is the easiest way to give the required amount of iron to infants? Is ferric ammonium citrate the best form? Should it be recommended routinely in well baby conferences, or should it be considered as a drug to be prescribed only by physicians? Would it be your opinion that the Children's Bureau should recommend the prophylactic use of iron in their publications?

DR. JEANS.—1. From our data it is indicated that when I teaspoonful of cod liver oil is ingested, the retention of calcium and phosphorus approaches closely or equals the maximum to be obtained. Presumably nothing is to be accomplished by larger amounts of vitamin D, and I teaspoonful of cod liver oil provides a sufficient margin of safety.

- 2. It is my opinion that the amount of vitamin D in irradiated milk as now produced is insufficient for the best nutrition of the infant and that additional vitamin D should be given. The requirement of the child past infancy is not known. It is the general belief that the child requires less than the infant, but the evidence for any belief is meager.
- 3. Much thought must be given to the infant's diet in order that sufficient iron may be obtained from food sources alone. It would seem a measure of safety to add one of the iron salts. Iron in the amount we have discussed could scarcely be considered harmful. Probably iron and ammonium citrate should not be stated as the best preparation, but it has seemed entirely satisfactory. The use of iron in the manner discussed should be considered from the nutritional point of view and could be recommended appropriately by anyone competent to give nutritional advice. I know of no reason why the Children's Bureau should not recommend the prophylactic use of iron if the director so desires.

DR. FRANK H. DOUGLASS (SEATTLE, WASH.).—When can we stop giving cod liver oil? When does rickets stop?

DR. JEANS.—It is our own preference to continue the use of cod liver oil throughout the period of childhood. The additional amount of both vitamins A and D may be considered advantageous.

Though rickets of the type caused by vitamin D deficiency is uncommon after two years of age, increased, and presumably more desirable calcium retentions are obtained, at least during the winter months, when cod liver oil or some equivalent is ingested. Increased calcium retentions appear to have a direct relationship to the prevention of tooth decay, which is so prevalent in childhood.

- DR. FEINBERG.—1. What are the relative merits of vitamin D present in certified milk from cows on a ration of irradiated yeast and milk irradiated directly?
  - 2. Do you feel that additional vitamin D in form of cod liver oil is necessary?
- 3. Do vitamin D concentrates have the same effect as vitamin D in the form of cod liver oil?
- 4. The iron question is very interesting. Do you feel that the comparatively small dose of iron and copper, such as is present in some of the proprietary sugars, as Abbott's cofron-maltose, is sufficient to prevent a negative iron balance during the first few months of life?
- 5. Are large doses of iron given to the mother during the latter months of pregnancy effective in preventing nutritional anemia in the infant?
- DR. JEANS.—1. Yeast milk is usually produced with 430 U. S. P. units of vitamin D to the quart and irradiated milk, with 135 units to the quart. Some have considered that the relative value of these two milks is directly proportionate to the vitamin D unitage. Even if yeast milk proves to be less potent than irradiated milk, on a unit-for-unit basis, the difference is not great and a marked advantage still exists in favor of yeast milk because of the greater vitamin D content.
- 2. It is my opinion that the amount of vitamin D in irradiated milk is not sufficient to meet the needs of the infant and consequently additional vitamin D from some source is indicated. The amount of vitamin D in yeast milk probably is sufficient.
- 3. For all practical purposes, it may be stated that vitamin D concentrates have the same effect as the vitamin D of cod liver oil. When the dose is reduced to minimum levels the probability that vitamin D of vegetable source is less potent than that of animal source must be considered. It is generally agreed that at the minimum effective level more units as viosterol are required than as cod liver oil. With customary dosages, however, this difference need not be considered because both materials are commonly administered above the level which produces the maximum physiologic effect. In considering a choice among vitamin D preparations, one should not lose sight of a possible need for vitamin A.

- 4. I do not know the iron content of cofron-maltose, but if it supplies 10 to 25 mg. of iron a day, as I believe it does, this amount of iron is ample not only to prevent a negative balance but also to allow a good retention after two months of age. A negative balance during the period of hemoglobin destruction in the first two months does not have the same significance as it does later.
- 5. The store of iron in the liver at birth depends appreciably upon the iron intake of the mother. When the mother's intake has been low the store of the infant may be negligible and also the amount of hemoglobin less than normal. On the other hand, the liver storage is not great under the most favorable conditions. The later storage from hemoglobin destruction is always greater and therefore more important than the amount present at birth. It has been found that ingestion of 20 mg, of iron daily by the mother during pregnancy permits ample storage for her and the infant.
- DR. EARL W. MAY (DETROIT).-1. Dr. Jeans, have you used irradiated milk higher than 135 units?
- 2. We have been using irradiated milk with 150 units and have found it most effective in the prevention of rickets and the maintenance of normal growth in the normal full-term infant.
  - DR. JEANS.-1. We have not. Such a milk has not been available to us.
- 2. The difference between 135 and 150 units to the quart is not great, and a marked difference in results would not be expected.

What is normal growth? The growth curves of Stuart published in 1933 and of Kornfeld published in 1929 show greater rates of growth than those published by Baldwin in 1921. This indicates that nutritional conditions are improving. Even the more recent studies of Kornfeld and Stuart have included individuals who had been receiving poor nutritional care, as well as those whose care had been good. Perhaps we should think of the ideal growth curve only in terms of good nutritional and hygienic care. In such case the rate of growth will be greater than that recorded in the Stuart and Kornfeld studies. Thus, good or optimal growth represents more rapid growth than the published averages now available.

- DR. BLATT.—Three children in my practice receiving vitamin D milk have had gastrointestinal disturbances associated with diarrhea. Their diarrhea ceased on ordinary pasteurized milk, but they did not progress as satisfactorily as do most of the children whom we feed without the use of this irradiated product. They were more irritable, muscle and bone development was not as satisfactory, nor did they have the regularity of weight curve increase which I am accustomed to see in my practice.
  - DR. JEANS.—We have had no experience with irradiated milk causing diarrhea.
- DR. ROGER MOORE (St. Joseph, Mo.).—Dr. Jeans stated that 1 dram of cod liver oil was sufficient. Will there be a deficiency of vitamin A in such a dose?
- DR. JEANS.—I do not know the infant's requirement for vitamin A, but there has been no obvious evidence of vitamin A deficiency with such a dose.
- DR. F. W. SCHLUTZ (CHICAGO).—What is the comparative prevalence of night blindness in urban and rural children, and what relation has this prevalence to the diet?
- DR. JEANS.—In our survey of Iowa children subnormal dark adaptation was found in 26 per cent of the strictly rural group, 53 per cent of the village group, and in from 56 to 79 per cent of the urban group, the variation in the last group depending upon the economic level. It may readily be assumed that the prevalence found has a direct relationship to the type of diet, inasmuch as improvement in the diet nearly always corrects the difficulty.

- DR. BLATT .-- 1. Is night blindness higher in cases with infection?
- 2. Does carotene drop in the winter?
- DR. CLAUSEN.-1. Cases with infection have a low carotene perhaps due partly to lack of appetite.
- 2. Carotene is low in the winter and rises in March and April to a plateau with a slight rise and then a fall to January.
  - DR. DURAND .- 1. How old were the children with night blindness?
  - 2. Did any children with night blindness get cod liver oil?
  - 3. Did you find more infection in the group with night blindness?
- DR. JEANS.—1. The ages of the children with night blindness ranged from six to fourteen years. Children at other ages were not examined.
  - 2. None of the children with night blindness were receiving cod liver oil.
- 3. No observations were made concerning the incidence of infections in children with night blindness.
- DR. WHEELER.—I should like to ask Dr. Jeans if after further observation on vitamin A experimentation he is still of the opinion that mineral oil destroyed the absorption of vitamin A in the intestine.
- DR. JEANS.—Mineral oil has a very decided effect in depleting the body of vitamin A, particularly when the intake of vitamin A is low or borderline as compared to the probable requirement.
- DR. WHEELER.—Can the photometer test be used as a standard for determining vitamin A deficiency?
- DR. JEANS.—The photometer is used as a means for detecting abnormal dark adaptation. Poor adaptation is caused by vitamin A deficiency in most, but not in all, instances. With these few exceptions, which are recognizable by ophthalmologic examination, the photometric test can be used as a standard for determining vitamin A deficiency. A new photometer is now available, which permits greater precision and ease of use than the one formerly employed.
- DR. DOUGLASS.—What is carotene besides vitamin A and pigment? I ask this question because of the favorable results we have seen in cases of albinism in which the administration of carotene in oil has increased the color of the retina. Is it due to pigment or vitamin A?
- DR. CLAUSEN.—The several isomeric carotenes are produced only by plants. They are hydrocarbons with the formula  $C_{40}H_{20}$ . One molecule of beta-carotene is transformed in the animal into two molecules of vitamin A, an alcohol with the formula  $C_{20}H_{20}OH$ . It is not yet known whether carotene as such performs any special function in the animal body aside from its function as precursor of vitamin A. When large quantities of carotene are ingested, especially when the carotene is not destroyed, the skin may become pigmented; it is possible that the retina may share in this pigmentation and that the process would be more apparent in an albino than in a normal person.
- DR. MARGARET NICHOLSON (WASHINGTON, D. C.).—Is cod liver oil better than viosterol? Does the absence of vitamin A in viosterol make a difference?
- DR. CLAUSEN.—Comparative studies by Hess and Lewis indicated that infants receiving cod liver oil had about as frequent and severe infections as infants receiving viosterol and that large additions of vitamin A to the diet in the form of carotene or halibut liver oil conferred no increase of resistance to infection. They concluded that the milk of the diet furnished enough vitamin A. However, most

of the infants studied by them were over six months of age. We have, therefore, compared the incidence and severity of infection in infants who received cod liver oil at least from the third month with the incidence and severity of infection in infants who did not, and we have found an apparent considerable increase of resistance during the latter half of the first year of life. Our work is open to the criticism that other factors than lack of vitamin A may play rôles in the control group of infants. I feel that your question can be answered only when we know more about the requirements for vitamin A in the early months of life.

DR. MAURICE J. LONSWAY (St. Louis).—I should like to ask Dr. Jeans if he has seen any bad effects with larger doses of iron. We give larger doses than he advises to premature infants, and it is our impression that they do quite well with no observable ill effects.

DR. JEANS—Doses in excess of 25 mg. a day probably will do no good. We have observed no actual harm from larger amounts, but we have not studied the metabolic effects in detail.

DR. BLATT .- Do premature infants retain iron?

DR. JEANS.—They break down hemoglobin during the first two months and do not need iron during this period. The prematurely born infants we have studied have retained ingested iron after two months of age.

DR ABT .-- 1. Do you still believe in Bunge's conception of the iron reservoir in the liver at birth?

- 2. Were the children who had a negative iron balance on breast milk or cow's milk?
- 3. Was the specific dynamic action of protein taken into account in the values you gave for creatinine excretion?
- 4. Are there any references in the literature as to the absorption of cod liver oil? It is not an uncommon experience, in calling at the homes of my patients, to have the mother show me the baby's diaper containing the stool and often a distinct separate oily substance which looks and smells like cod liver oil. When we state the optimal dose, must we not then allow for the amount of nonabsorbed oil (if a portion of the oral dose is not absorbed)?
- 5. Are there any other experiments recorded in the literature besides those which Dr. Jeans mentioned which substantiate the statement that spinach is a demineral izer?
- DR. JEANS—1. Apparently a small store of iron exists normally in the liver at birth. However, this store is relatively unimportant when compared to the amount of iron which becomes available from the destruction of hemoglobin in the early weeks after birth.
  - 2. The infants with a negative iron balance were receiving cow's milk.
- 3. No, this was not considered. It is probable that this factor relates more closely to creatine than to creatinine exerction.
- 4 I am not familiar with the literature on this subject. My statements concerning the dose of cod liver oil were based on the usual or average utilization. In my own experience, failure of utilization has been exceptional. In such a case it seems doubtful that increase of the intake will increase the absorption. Some other source of vitamin D would seem indicated.
- 5. Dr. Schlutz and his coworkers have pointed out the lack of value of spinach as a source of iron for infants (J. Pediat 3: 225, 1933).

Di H. G. Poncher, Chicago, Ill. Recorder.

### Academy News

The annual meeting of Regions I and II of the American Academy of Pediatrics will be held in Baltimore, Md. The headquarters will be at the Belvedere Hotel, Charles and Chase Streets. The following men are in charge:

Louis C. Schroeder, New York, N Y., Chairman, Region I; Phillip Van Igen, New York, N Y, Acting Chairman, Region I, Edward Clay Mitchell, Memphis, Tenn., Chairman, Region II; Baltimore Committee on Arrangements, Fred B Smith, Chairman, L Emmett Holt, Jr, C Loring Joshn, J. H Mason Knox, Jr, D. C Wharton Smith.

The following program has been announced

#### MONDAY, NOVEMBER 16

9.30 AM Hurd Auditorium, Johns Hopkins Hospital.

An Unusual Type of Bone Dystrophy Resembling Paget's Disease, With Presentation of a Case—Dr. Laslo Kajdi.

Presentation of Two Cases of Porphyria-Dr. Harriet G. Guild.

Certain Aspects of Serum Therapy in Meningococcus Meningitis— Dr. Francis F. Schwentker.

A Study of the Rate of Growth and Osseous Development in Hypothyloidism and Dwarfism—Dr. Lawson Wilkins

Newer Concepts of the Achondroplastic State-Dr Walter Block.

The Treatment of Gonococcal Vaginitis With Amniotin-Dr. Richard W. TeLinde.

The Cause of Icterus Neonatorum-Dr. Nicholson J. Eastman.

Observations on Hypertension in Childhood, With Particular Reference to the Rheumatic State—Dr. Helen B. Taussig

Renal Hyperparathyroidism-Dr Edwards A. Park

Child Hygiene Program in Maryland-Dr. J. H Mason Knox and associates

12:30 NOON Luncheon and meeting of state chairmen, Belvedere Hotel.

1 00 P.M. Luncheon at Welch Memorial Library

2.00 PM X ray Changes and Prognosis in Pulmonity Tuberculosis in Young Children-Dr. Miriam E Brailey.

Experiences With Suipestifer Infection in Childhood-Dr. John A. Washington

A Study of Chronic Nephritis in Childhood—Dr Alexander J. Schaffer.

Experiences With Esophage il Injury Pollowing the Ingestion of Corrosives—Dr R Campbell Goodwin.

The Surgical Treatment of Bronchiectusis-Dr William F. Rienhoff, Jr

The Possibilities of Active Immunization Against the Pneumococcus in Different Age Groups—Dr. Lloyd D Felton

Congenital Reading Disability-Dr Leo Kunner and Dr. Angus L

The Study of the Anemic Child-Dr. Hugh W. Josephs

A Study of the Causes of Xanthochromia in Spinal Fluid-Dr. Frank H Robinson, Jr.

Essential Familial Lapenia-Dr Francis X. Aylward and Dr L Emmett Holt, Jr.

7 00 1 M Annual banquet at Belvedere Hotel

#### TUISDAY, NOVEMBER 17

9:30 AM. Wilson Memorial Amphitheatre, University of Maryland Hospital Intracranial Hemorrhage of the Newborn. With Presentation of Cases Previously Treated—Dr. C. Loring Joshin

Clinical Pathological Discussion of Birth Hemorrhage—Dr. Charles Bagley.

Hypertension Associated With Embryonal Adenosarcoma. A Report of Three Cases—Dr J. Edmund Bradley.

A Study on the Feeding of Whole Milk, Acidified Milk, and Gelatinized Milk, With Especial Reference to Calcium and Phosphorus Absorption—Dr. I. Meranski

Banana Therapy in Diarrheal Diseases-Dr Thomas A Christensen

Acute Empyema in Children-Dr. Cytus Horine

Xanthomatosis of Bone-Dr Allen Voshell

The Vitamin B Complex An Experimental and Clinical Study With Special Reference to Growth and Constipation—Dr. A. H. Finkelstein

Complications of Accessory Nasal Infections in Children-Dr. Edward A Looper

Presentation of a Case of Spontaneous Pneumothorav-Dr. Edgar Friedenwald and Dr Bowers Mansdorfer

Persistent Pyuria, Due to Congenital Urethral Malformation: A Case Report—Dr Fred B Smith and Dr. A. J Gillis

2 00 P.M Regional business meetings to be held separately. There are a number of important questions to be decided. This is probably the most important session of the regional meeting. It is earnestly requested that all members in attendance at the general meeting be present.

The annual meeting of Region III will be held in Cincinnati, Ohio, Nov. 20 and 21, 1936, with headquarters at the Netherland Plaza Hotel In addition to the scientific program given in three sessions, there will be a dinner on Friday evening at the Netherland Plaza Hotel with an interesting program

The following scientific program has been announced

#### FRIDAY, NOVEMBER 20

10 00 AM to 12:00 Noon Netherland Plaza

Use of Supravital Technic in Studying Children's Diseases—C. R. Rittershofer

Significance of Albumin Globulin Ratio in Nephrosis—H W. Robinson Relation of Hemoglobin Content and Red Cell Size to Age and Nutritive Condition—George M. Guest.

Hypoglycemia Versus Hyperinsulinism-Stanley Dorst

Stimulation With Histamine on Gastric Flow-Leon Schiff.

On Significance of Repeated Tuberculin Tests—Waldo E Nelson Alkalosis—Glenn E Cullen

2.00 PM to 4.45 PM

Diagnosis and Treatment of Irritative Symptoms of the Central Nervous System of the Newborn—Harold F. Downing

The Premature Department of the Cincinnati General Hospital—Edward A. Wagner

Behavior Problems of Children-E A. North

Possible Relation of Various Types of B Coli to Enteritis-Merlin L. Cooper.

Benign Lymphocytic Meningitis (Aseptic Meningitis)—Frank E. Stevenson, Robert A. Lyon, and Clyde Dummer.

Epidemic of Pleurodynia in Children in the Summer of 1935—Robert McDonald, Barbara Hewell, and Merlin L. Cooper.

Pellagra in Children and Present Status of Pellagra—Tom D. Spies. Vitamin D Content of Serum—Josef Warkany.

Relation of Liver to Ketosis-I. Arthur Mirsky.

#### SATURDAY, NOVEMBER 21

10:00 A.M. to 12:00 NOON. Children's Hospital Research Foundation Auditorium.
A Case of Congenital Heart Disease With Familial History—Robert
H. Kotte.

Method of Blood Matching for Transfusions-Paul Hoxworth.

Report of an Unusual Condition Involving the Bones in a Ten-Year-Old Boy-Leo S. Friedman,

A Case of Unilateral Communicating Hydrocephalus Improved by Ureteral Dural Anastomosis—J. Victor Greenebaum and Henry Freiberg.

Connection Between Pyarthrosis of the Hip Joint and Pelvic Abscesses— Albert H. Freiberg and Joseph A. Freiberg.

The Diagnostic Use of Specific Antiserum in Intradermal Tests—Lee Foshay.

Relation of Endocrine Disorder to Hereditary Deviations-Josef Warkany and A. Graeme Mitchell.

The fifth annual meeting of Region IV was held on Oct. 22 to 24, 1936, in San Francisco, Calif. An interesting scientific program was presented, and a business meeting for the Region was held. Dr. Karl F. Meyer was invited to speak on "Neurotropic Viruses and the Diseases Caused by Them."

Dr. Dorman E. Lichty, of Ann Arbor, Mich., has just been elected a member of the Academy.

Dr. N. N. Allen, of Houston, Texas, died on Sept. 22, 1936. Dr. Allen was a fellow of the Academy and was one of the pioneers in pediatrics in Texas. He was very much loved in Houston and was a great friend of the young men.

Dr. Charles Schott, of Chicago, Ill., died Oct. 1, 1936. He was a fellow of the Academy of Pediatrics.

Dr. Robert K. Rewalt, of Williamsport, Pa., a well-known pediatrician of that state, died suddenly July 27, 1936. Dr. Rewalt was a fellow of the Academy of Pediatrics.

The following appointments have been made by the Executive Board:

Dr. A. Graeme Mitchell, of Cincinnati, to the chairmanship of the Committee on Nursing Education. Dr. Lucas resigned the chairmanship but remains on the committee.

To the Committee on Medical Education, Subcommittee on Postgraduate Education: Dr. George M. Lyon, Huntington, W. Va., chairman; Dr. Horton Casparis, Nashville, Tenn.; and Dr. Hugh L. Dwyer, Kansas City, Mo.

The Michigan Section of the American Academy of Pediatrics held its fall meeting on Sept. 24, 1936. The members attended the meetings of the Pediatric Section of the Michigan State Medical Society on September 24 and 25.

Preceding the meeting a dinner was held at the Hotel Statler in Detroit. Thirty members were present to honor R. Cannon Eley. of Boston, who was in Detroit to speak before the Michigan State Medical Society. Following dinner, reports of the committee appointed to cooperate with the State Health Department on matters pertaining to the Social Security Act and the Committee on Postgraduate Education were read and approved.

The members decided to hold the next meeting in January in conjunction with the meeting of the Detroit Pediatric Society.

Edgar E. Martmer, chairman for Michigan, announced the complete reorganization of the department of pediatrics at Wayne University, Detroit, and the accept ance of the position as head of the department of pediatrics by Thomas B. Cooley, past president of the American Academy of Pediatrics.

#### News and Notes

A bulletin announces the postponement of the Fourth International Congress in Pediatrics. The date is now definitely set for Sept. 27, 28, 29, and 30, 1937. The Congress probably will be followed immediately by the Second International Congress for the Protection of Infancy. Dr. L. Emmett Holt, Jr., Baltimore, is secretary of the American committee.

The Central New York Pediatric Society held its fall meeting in Schenectady on October 1. A clinical program was presented at the Ellis Hospital, and after a business meeting at the home of Dr. Frank Van Der Bogert, president of the Society, a dinner was served at the Mohawk Club. Dr. Whitney, of the General Electric Company, addressed the dinner meeting.

Pediatricians from Rochester, Auburn, Watertown, Utica, Schenectady, Albany, Troy, and Syracuse were present.

On September 19 the Subcommittee on Child Hygiene of the Committee on Public Health and Medical Education, New York State Medical Society, held a meeting in New York City with Dr E S Godfrey, commissioner, state department of health, several officers of the state Society, and a small group of pediatricians

The plan of the meeting was to outline a program on child hygiene through the various county societies

A radio forum entitled "Growth and Development of the Child" will be given under the joint auspices of the National Congress of Parents and Teachers, the American Academy of Pediatrics, and the National Broadcasting Company.

#### COMMITTEE

Mrs. B. F. Langworthy, president, National Congress of Parents and Teachers, Chicago; C. A. Aldrich, M.D., Winnetka, Ill, and Henry F. Helmholz, M.D., Rochester, Minnesota, representing the American Academy of Pediatrics; Miss Judith C.

Waller, director of education, central division, National Broadcasting Company, Chicago; Mrs. John Sharpless Fox, Chicago, representing the radio forum committee of the Congress.

- 1. Oct. 21, 1936 Introductory: What Is Growth?-Lawrence K. Frank.
- 2. Oct. 28, 1936 Prenatal Growth-George L. Streeter.
- 3. Nov. 4, 1936 Growth of Infants-Harry Bakwin.
- 4. Nov. 11, 1936 Growth of the Adolescent-Horace Gray.
- 5. Nov. 18, 1936 Growth of Organs-R. E. Scammon.
- 6. Nov. 25, 1936 Our Ancestors-E. A. Hooton.
- 7. Dec. 2, 1936 Does Like Beget Like?—Amos H. Hersh.
- S. Dec. 9, 1936 Measurements of Growth-Harold C. Stuart.
- 9. Dec. 16, 1936 Individual Variations in Infants and Children—Alfred H. Washburn.
- 10. Dec. 23, 1936 Foods and Growth-E. V. McCollum.
- 11. Dec. 30, 1936 Chemical Elements and Their Part in Body Growth—S. Z. Levine.
- 12. Jan. 6, 1937 Energy and Growth-A. A. Weech.
- 13. Jan. 13, 1937 Our Glands-R. G. Hoskins.
- 14. Jan. 20, 1937 The Action of Glands on Growth-Oscar Riddle.
- 15. Jan. 27, 1937 Effects of Light, Sun, and Other Rays on Growth-Otto Glasser.
- 16. Feb. 3, 1937 Heredity or Environment?-E. C. MacDowell.
- 17. Feb. 10, 1937 How the Mind Grows in Infancy-Arnold Gesell.
- 18. Feb. 17, 1937 How Children's Minds Grow-Walter R. Miles.
- Feb. 24, 1937 The Importance of Music for Growing Children—Walter Damrosch.
- 20. Mar. 3, 1937 Emotional Development in Children-John E. Anderson.
- 21. Mar. 10, 1937 The Connection Between Mind and Body Growth—Bert I. Beverly.
- 22. Mar. 17, 1937 Fitting the Course of Study to the Child's Mental Development—Carleton Washburne.
- 23. Mar. 24, 1937 Education and Mental Growth-Frank N. Freeman.
- 24. Mar. 31, 1937 Athletics, Exercise, and Fatigue in Growing Children—D. B. Dill.
- 25. Apr. 7, 1937 Physical Education for Growing Children-C. W. Savage.
- 26. Apr. 14, 1937 Disease and the Doctor's Side of Growth-Joseph Brennemann.
- 27. Apr. 21, 1937 Disease and the Doctor's Side of Growth—Joseph Brennemann.

  The Effects of Family Income on a Child's Growth—Martha
  M. Eliot.
- 28. Apr. 28, 1937 The Effect of Child Labor on Growth-Richard A. Bolt.
- 29. May 5, 1937 Growth of Children During Wars and Depressions-Carroll E. Palmer.
- 30. May 12, 1937
   31. May 19, 1937
   32. Health Hazards in the Period of Growth—Louis I. Dublin.
   33. May 19, 1937
   34. Health Hazards in the Period of Growth—Henry E. Sigerist.

Editor, Norman C. Wetzel, M.D., Babies and Childrens Hospital, Cleveland, Ohio. Music selected and arranged by Leon Machan, pianist, Cleveland Symphony Orchestra.

Dr. R. Langley Porter retired as dean of the School of Medicine, University of California, San Francisco.

Dr. W. McKim Marriott, of St. Louis, was appointed dean of the School of Medicine and professor of experimental research. University of California, San I'rancisco. Dr. Marriott, who succeeds Dr. Porter, assumed his duties on July 1, 1936.

Dr. Alexis F. Hartmann, of St. Louis, was appointed professor of pediatrics, School of Medicine, Washington University, and chief of staff of the St. Louis Children's Hospital. Dr. Hartmann succeeds Dr. Marriott. Dr. Hartmann assumed his duties on July 1, 1936.

The American Pediatric Society will hold its next annual meeting at University, Virginia on April 29, 30, and May 1, 1937.

The following men have been certified by the American Board of Pediatrics since the last report.

Harry S. Altman, New York, N. Y.
Louis Barash, New York, N. Y.
Walter Douglas Brown, Beaumont, Texas
Fred W. Bush, Rochester, N. Y.
Nicholas Boddie Cannady, Dothan, Ala.
Charles Rowse Dengler, Jackson, Mich.
R. Bruce Eldredge, Omaha, Neb.
Edward Porter Essertier, Hackensack, N. J.

George Julius Feldstein, Pittsburgh, Pa. Alfred Elias Fischer, New York, N. Y. Edward O. Fitch, Houston, Texas James LeRoy Foster, Pittsburgh, Pa. Hugh C. Graham, Tulsa, Oklahoma Theodore P. Herrick, Cleveland, Ohio George Russell Irving, New York, N. Y. Sidney David Kramer, Brooklyn, N. Y. Alfred Gustav Langmann, New York, N. Y.

George P. Laton, Los Angeles, Calif. Mathilde Loth, New York, N. Y. Mary Schwartz Newman, Brooklyn, N. Y. Maurice J. Searle, Tulsa, Okla. Harry M. Shapiro, New York, N. Y. Edwin August Socola, New Orleans, La. Edwin B. Weldon, Bridgeport, Conn.

## **Book Review**

The Adopted Child. ELEANOR G. GALLAGHER, New York, 1936, Reynal and Hitchcock, p. 291. Price \$2.50.

This is a disappointing book. As a "first book" on an important subject frequently brought to the pediatrician for discussion, it merits more of a review than the book inherently justifies. According to the cover blurb, it is a "complete book" for the general reader, as well as a "handbook" for social workers, adoption agencies, etc. It fails to fulfill in a satisfactory way any one of these purposes, let alone all. There are a number of excellent chapters, as the historical introduction and the summary of state laws relating to adoption in the appendix. Rather than the sound critical discussion which we are led to expect, the book as a whole turns out to be a somewhat emotionally biased special plea for the immediate separation of the illegitimate child from the mother, its immediate placement in an adoption nursery, and its placement into the adopting home when the baby is a few weeks old. There is much to be said in favor of this, but there is another viewpoint held by many intelligent and experienced people. Rather than critically presenting the other viewpoint, which should be done in a "complete book" on the subject of adoption, the author indulges in an uncalled for tirade against trained social workers and cites a few stupid actions of trained workers to prove their incompetence as a whole, simply because they disagree with the author's viewpoint-a fallacious and silly argument, as an equal number of stupid actions could be cited in regard to volunteer workers. Since some trained workers do not agree with the author's views and are responsible, in her opinion, for laws requiring maternal nursing for a few months, away with the whole tribe of them. Since intelligence tests are not available for young infants, the author attempts to show intelligence tests are of no value and simply displays a rather limited appreciation of their value and functions. By a few citations from literature she attempts to show that artificial feeding is the equivalent or even superior to maternal nursing. Thus the book becomes a special plea to uphold a viewpoint rather than a sound balanced discussion of the subject of adoption.

We are not informed as to the author's training, qualifications, and connections, except that we are told that she has had many years of experience in adoption work. The reviewer would hazard from the text that it has been in connection with the Cradle in Chicago. The excellent work of the Cradle is well known and scarcely needs the defensive attitude of the author. She further refers to the splendid work of Dr. Chapin and his wife in New York and the Spence organization, and then rather naively remarks that, although there are many other adoption nurseries scattered throughout the United States, she is unfamiliar with them. Excellent as the work of the Cradle undoubtedly is, it scarcely gives a broad enough background to cover the entire field of adoption with its many problems. The chief criticism against the adoption nurseries is that so far they have not taken advantage of their unique opportunity to make a careful critical scientific study of the development of the infants they have placed. Such a study would do more to show the value, or weakness, of the ideas the nuthor defends than these many pages of personal opinion.

The value of giving in detail the Dick technic is decidedly questionable in a book for the parent or general reader. Physicians will agree with the author that the child should be told it is adopted. The child, however, should have been told long before he could have understood the "precious" letter with which the author concludes the discussion of this topic.

The book is neither fish, flesh, nor fowl. If the emotionalism and non-germane controversial matter had been omitted and the title changed to "Adoption Nurseries" the book would have a place. But labeled as a "complete book" on the subject of adoption, it goes under false colors, and the reviewer feels it an unwise book for physicians to recommend to uncertain minded and noncritical parents who are considering the problem of adoption.

#### Errata

In the article by Martha M. Eliot et al. entitled "A Study of the Comparative Value of Cod Liver Oil, Viosterol, and Vitamin D Milks in the Prevention of Rickets and of Certain Bisic Factors Influencing Their Efficacy" in the September issue, the following corrections should be made

On page 361 the last sentence above the illustration should appear as the last sentence of the first footnote.

On page 363 the following paragraph should be inserted after line 11:

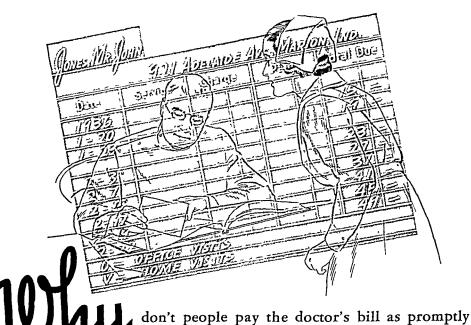
"It should be pointed out that the incidence of rickets among the colored infants is consistently lower than among the white infants when the total groups given the different types of antirachitic agents are considered and that the same tendency exists with few exceptions at the different dosage levels for each agent."

On page 371 the footnote to Table X should read:

"Code: A,-, B,-, very slight," etc.

In the article, "The Problem of Dental Caries With Relation to Bacteria and Diet," by Philip Jay, M.S., D.D.S., which appeared in the June, 1936, issue of the Journal, on page 729, line 44, the word "negative" should be "positive"; thus the sentence should read: "It was subsequently observed that the same proportion of caries free individuals contained L. acidophilus agglutinins in the blood serum, whereas 70 per cent of the susceptible persons tested yielded positive skin tests and contained either no demonstrable acidophilus agglutinins or else agglutinin titers which were much lower than was ordinarily found in the caries free"

In the article, "The Premature Infant," by William W. Swanson, M.D., Vernon E. Lennarson, M.D., and Fred L. Adair, M.D., which appeared in the July issue of the Journal, the reference to Dr. Blackfan on page 15, line 41, is incorrect. His name should not have been mentioned in connection with the treatment by in jecting whole blood intramuscularly.



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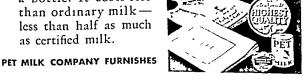
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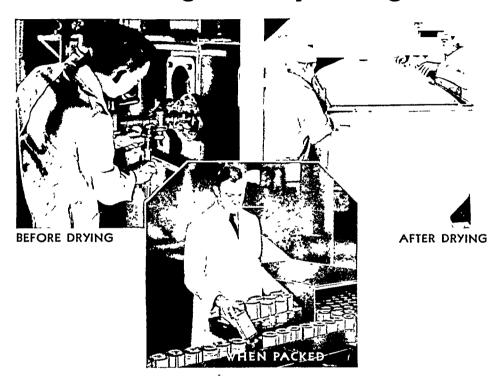
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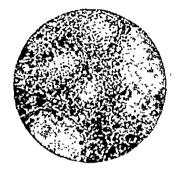
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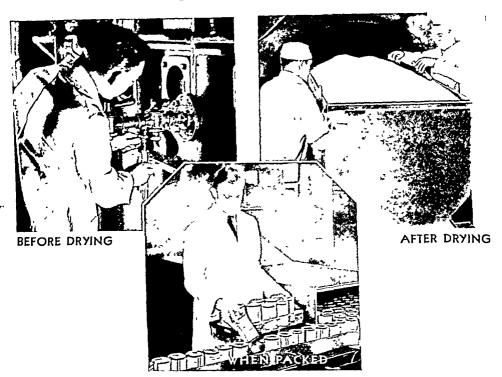
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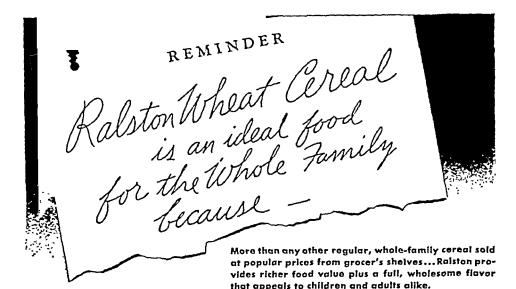
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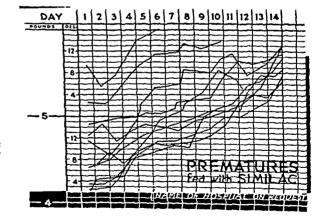
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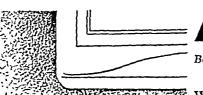
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The Doctor Regulates

Bottle Feeding

INTANTS should be weaned from the breast at eight months. The season of the year is immaterial with modern knowledge of nutrition and hygiene. Gradual weaning is desirable. It is accomplished by progressively increasing the number of bottle feedings in substitution for the breast feedings.

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The formula in abrupt weaning prepared for the entire day consists of 24 ounces milk, 8 ounces water, 3 tablespoons Karo, divided into 4 feedings, 8

Feeding	1st Week	2nd Week	3rd Week	4th Week
6:00 A.M.	Breast	Breast	Breast	Bottle
10:00 A.M.	Breast	Breast	Bottle	Bottle
2:00 P.M.	Breast	Bottle	Bottle	Bottle
6:00 P.M.	Bottle	Bottle	Bottle	Bottle

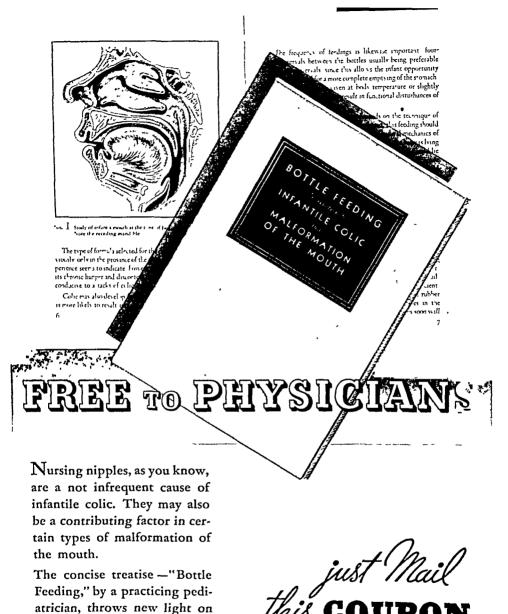
ounces each, at 4 hour intervals. The formula can be concentrated once the baby is adjusted to the bottle feeding.

Karo is a mixture of dextrins, maltose and dextrose (with a small percentage of sucrose added for flavor) practically free from protein, starch and minerals. Karo is a non-allergic carbohydrate, not readily fermentable, well tolerated, readily digested, effectively utilized and economical for both the baby and the budget.





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several important points in this

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Dr. Grover F. Powers, New Haven, Conn., discusses carbohydrates in a recent article on "Infant Feeding." We quote in part:

"Too much emphasis has been placed on the fact that the milk sugar of all animals is lactose." .... "If milk is the basis of the infant's food, the lactose so given almost certainly meets the minimum requirements for that substance ...."

"The advantages of a mixture of added carbohydrates, when any but small amounts are used, probably rest on solid ground. Since a variety of enzymes are required for the digestion of a variety of carbohydrates, the absence or reduction in amount of any specific enzyme will likely be associated with less digestive disturbance if this food element

is fed as a mixture of small amounts of several carbohydrates rather than as a large amount of a single sugar or starch. Moreover, under such circumstances the availability of the products for absorption is spaced, the varied influences on bacteria and yeast of different nutrients are achieved, and the hydragogic effect of the milieu is lessened . . . ."

"Laxative effects are probably promoted by increasing the relative proportion of malt sugar over others, but it is important to recall in this connection that many of the commercial products containing maltose are mixtures not only of sugar and starch but of salts and other substances largely unidentified, which may well cause the laxative action."

—Journal A.M.A.—756; Vol. 105, No. 10; Sept. 7, 1935.

Cartose contains no irritating organic or inorganic impurities to cause laxative action. Cartose has introduced a new standard of bacterial purity, and is made expressly for the physician.

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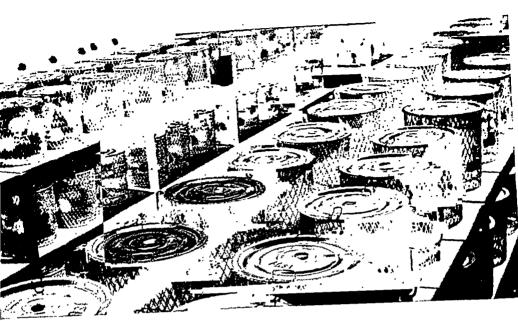
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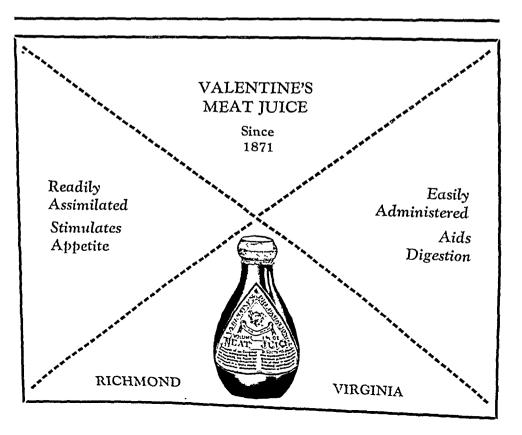


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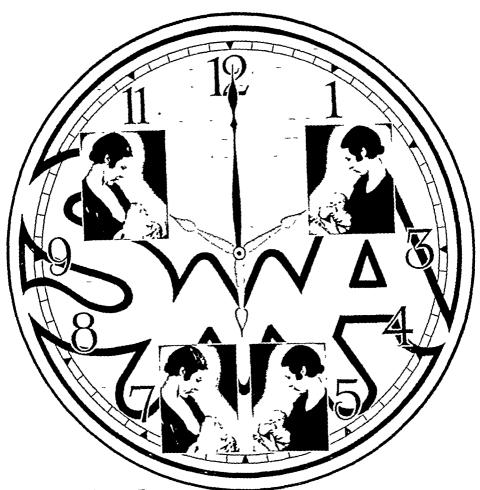
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- \* Diseases of Infancy and Childhood, New York, Appleton-Century, 1933.
- \*\* The Infant and Young Child, Philadelphia, Saunders, 1929.
- \*\*\* Feeding and t' N ... Childhood, Pt
  The Infant ar 1929.

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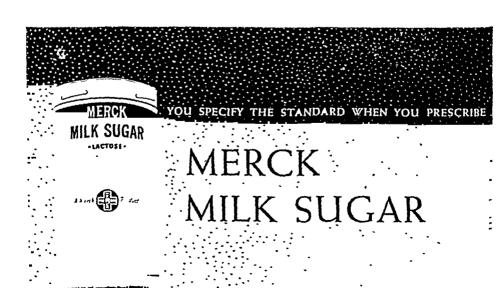


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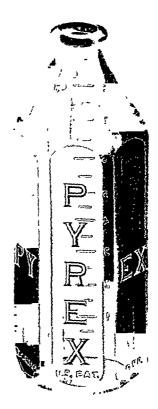
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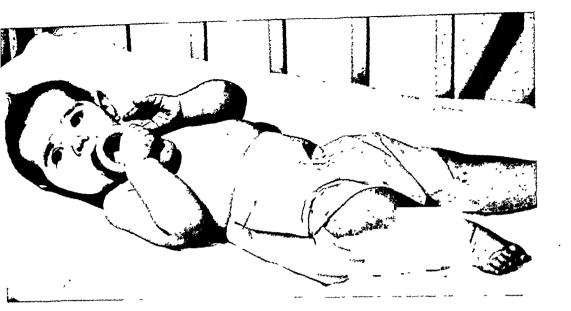
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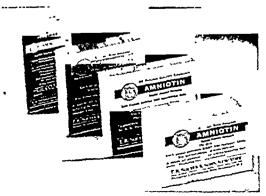
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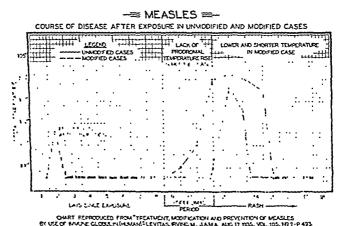
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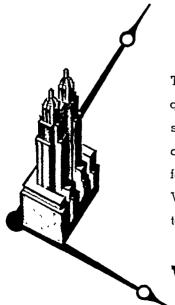
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Libby's special homogenization completely breaks up food cell walls—exposes nutrients to enzymes for easy, complete digestion.

... breaks up cells in solid foods...releases nutrients for easy, quick digestion

THESE two drawings show why Libby's Baby Foods are so much easier for infants to digest ... and why they provide far greater nourishment ... than the most carefully prepared strained foods.

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- (2) It completely breaks up whole food cells in solid foods...shatters the tough cellulose wall that encloses nutrients. Nutrients are exposed to digestive juices for easy, complete digestion. And yet all the bulk required for normal elimination is retained.

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Seventeen nourishing foods in only six tins. Leading nutritionists recommended that Libby combine three or more foods in each tin to give babies balanced values of vitamins, minerals and other food essentials.







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The importance of adequate nutrient values in the diet of those whose vigor has been sapped by illness cannot be over-emphasized. When you recommend strained foods, you do so in the hope that your patient will get the best in these health-giving values—the wholesome goodness of garden-fresh ingredients picked at their prime—cooked with care—sealed fresh in shining tins.

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The consistency of Heinz Strained Foods makes them easily digestible. They are widely recommended for infant feeding. For invalids—dissatisfied with restricted diets—the delicious flavor and nourishing goodness of Heinz Strained Foods bring renewed enjoyment to eating. Remember, your recommendation of Heinz Strained Foods is backed by the Seal of Acceptance. Don't hesitate to suggest them—by name!

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10 KINDS-1. Peas. 2. Carrots. 3. Prunes. 4. Spinach. 5. Green Beans. 6. Tomatoes. 7. Cereal. 8. Apricot and Apple Sauce. 9. Strained Vegtable Soup. 10. Beets.

### The Journal of Pediatrics

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No. 4

### Original Communications

FACTORS POSSIBLY INFLUENCING THE RETENTION OF CALCIUM, PHOSPHORUS, AND NITROGEN BY INFANTS GIVEN WHOLE MILK FEEDINGS

T. THE CURDING AGENT

P. C. Jeans, M.D., Genevieve Stearns, Ph.D., John B. McKinley, B.A., Eva A. Goff, B.A., and Dorothy Stinger, M.S. Iowa City, Iowa

NMODIFIED whole sweet milk is not readily digested by young infants, but abundant clinical observation now attests that whole milk acidified with lactic acid to the point of formation of a fine curd can be well utilized even by very young infants.<sup>1</sup> It is known that evaporated milk forms a fine curd in the stomach, a curd similar in many respects to that of human milk. Brennemann<sup>2</sup> has found that the clinical results were equally excellent when either acidified or unacidified evaporated milk was fed, and he has concluded that the fineness of the curd rather than decreased buffer capacity was responsible for the improved utilization.

A finely divided curd with its increased surface for action of digestive juices might be expected to increase the absorption and therefore the retention of nitrogen. It seems possible, however, that acidification of the milk might be an additional aid in the absorption of calcium. In order to determine the effect of the method of preparation of the feeding upon the retentions of nitrogen, calcium, and phosphorus, infants have been given boiled fresh whole milk feedings curded by means of lactic or citric acid or by the addition of a pepsin-rennin preparation, or evaporated milk untreated except for dilution to the equivalence of whole milk or slightly less for the younger infants. Each of these methods of preparation of the feeding permits the production of a fine curd in the infant's stomach, though the buffer value is altered appreciably only with the acid additions.

From the Department of Pediatries, State University of Iowa.

The expenses of this investigation were defrayed in part by Mead Johnson and Company, Evansville, Indiana.

The feedings of each type contained 6 per cent of added carbohydrate, consisting of a dextrin-maltose mixture. Each infant received one teaspoonful of cod liver oil daily, containing approximately 350 U.S.P. units of vitamin D. The customary additions to the diet were given each infant at the same age, viz., 1 ounce of orange juice was given daily to infants under four months of age, 2 ounces to older infants; an egg yolk was added to the feeding at four months, sieved vegetables were given at five months, and sieved fruits at six months.

The acid milks contained 4 to 4.5 c.c. of 85 per cent lactic acid or 10 c.c. of 25 per cent citric acid per liter. The pepsin-rennin prepara-

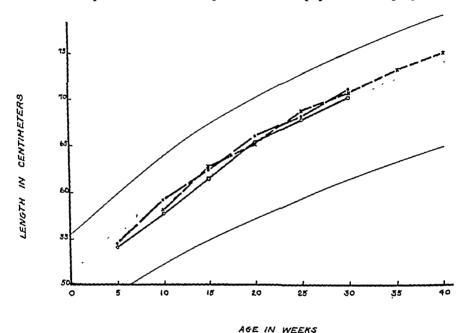


Chart 1.—Average growth in length of infants given feedings of whole milk with 6 per cent carbohydrate addition.

O————O Infants given milk acidified with organic acid.

Infants given milk curded with pepsin-rennin solution.

X----- Infants given unacidified evaporated milk.

X ---- X The shaded

represents the average range, and the fine lines the limit of portion normal of the Kornfeld growth standards.

tion used contained 2 c.c. of 85 per cent lactic acid per liter; 10 c.c. of the solution was added to a liter of milk, making the final added acid concentration less than 0.002 per cent. The effectiveness of this preparation may thus be ascribed wholly to the enzyme action. evaporated milk was diluted with an equal volume of 12 per cent carbohydrate solution for the older infants, and with two volumes of 9 per cent carbohydrate solution for the very young infant. to preclude, if possible, the necessity for use of protein for energy, the daily caloric intake of the infants was kept as high as practicable.

The average ingestion varied from approximately 140 calories per kilogram for the younger infants to 120 calories per kilogram for the older ones.

Four infants for varying lengths of time were given boiled fresh milk acidified with lactic acid, then citric acid was substituted for lactic acid; five other infants were given the citric acid milk exclusively. One infant received evaporated milk acidified with lactic acid. Eight infants were fed rennin milk mixtures, and four the unacidified evaporated milk feedings. Three of this latter group had previously been given acidified evaporated milk, and a summary of the findings has been reported.3

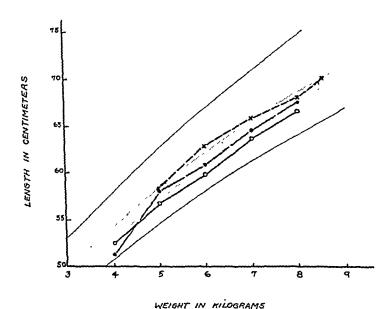


Chart 2.—Average growth in weight for length of infants given feedings of whole milk with 6 per cent carbohydrate addition.

Infants given milk acidified with organic acid. Infants given milk curded with pepsin-rennin solution. Infants given unacidified evaporated milk.

X - - - - X

The shaded portion represents the averege range, and the fine lines the limit of normal of the Kornfeld growth standards.

The general ward and laboratory procedures have been discussed in detail elsewhere.2 Accurate records were kept of growth, both in length and weight, and of muscular achievement at various ages: roentgenograms of wrist and ankle were obtained at four-week intervals. The metabolism periods were of three days' duration. analyses of food and exercta were made according to standard procedures; calcium was determined by a modification of the McCrudden technic,4 phosphorus by the method of Fiske and Subbarow,5 and nitrogen by the Kjeldahl-Gunning procedure.6

#### RESULTS

Clinically, all of the milk feedings used seemed equally effective. The stools of those infants fed the unacidified milks tended to be more formed in character than did those of the infants fed the acid milks. All of the infants grew both in length and weight, at somewhat greater rates than the average standards. No differences in rate of growth

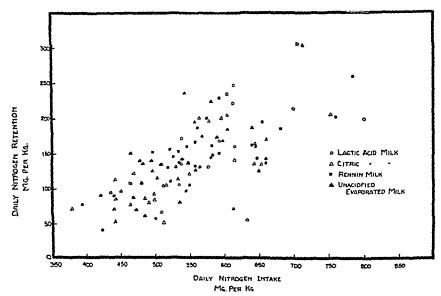


Chart 3.—The effect of the curding agent upon the retention of nitrogen by infants given whole milk feedings.

could be ascribed to the different diets. The average growth curves are shown in Charts 1 and 2. Bone growth and calcification, as evidenced by roentgenographic examinations, were normal for each infant.

TABLE I
URINARY EXCRETION OF CITRIC ACID BY INFANTS

NAME	ACID ADDED TO MUK	AGE WK,	CITRIC ACID INGESTED GM. PER DAY	AVERAGE URINARY EXCRETION CITRIC ACID GM. PER DAY
R—n	Lactic	18	1.57	0.191
		20	1.47	0.176
	Citric	28	3.85	0.189
Cr	Lactic	11	2.72	0.132
		13	1.98	0.138
	Citric	15	3.72	0.194
		18	5.02	0.150
Ge	Lactic	8	1.62	0.206
		10	1.71	0.184
	Citric	16	4.62	0.213
K-n	Lactic	7	1.56	0.088
	Citric	10	3.16	0.097

In order to determine the utilization of citric acid by infants, the citric acid excretion in the urine of four infants was studied when the infants were given lactic acid milk, and when the citric acid milk was

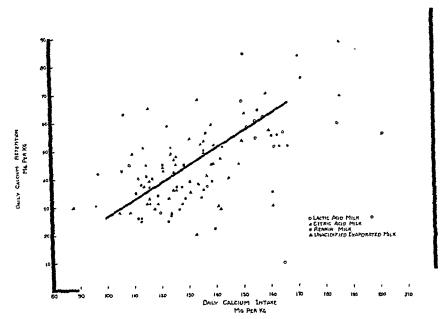


Chart 4.—The effect of the curding agent upon the retention of calcium by infants given whole milk feedings.

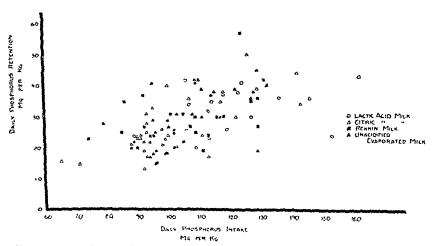


Chart 5—The effect of the curding agent upon the retention of phosphorus by infants given whole milk feedings.

fed. We are indebted to Dr. Adrian Kuyper, of the department of biochemistry, for these analyses. The results, given in Table I, demonstrate that the added citric acid was almost completely oxidized, causing no added burden to the kidneys.

TABLE DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGEN BY INFANTS

NAME	CURD	AGE	WFIGHT	LENGTH	CA IN-	1	CALCIUN EXCRETIO			CIUM NTION
DATE OF BIRTH	MODIFIER	WK.	GM.	CM.	TAKE TOTAL GM.	URINE GM.	FECES	TOTAL GM.	TOTAL GM.	PER KG.
R-n	L. A.*	12	5397		1.089	0.025	0.762	0.787	0.302	0.056
11/10/30		14	6130	60.0	1.132	0.018	0.755	0.773	0.359	0.059
		16 18	$6552 \\ 6925$	$61.0 \\ 62.1$	0.937 $1.046$	0.023	0.525	0.548	0.389	0.060
		20	7455	63.8	0.810	$0.017 \\ 0.034$	$0.567 \\ 0.444$	$0.614 \\ 0.478$	$0.432 \\ 0.332$	$0.063 \\ 0.045$
	C. A.†	22	7512	65.7	0.884	0.034	0.524	0.548	0.336	0.045
	0,	24	7712	67.0	0.848	0.019	0.426	0.445	0.330	0.049
		28	8300	68.4	1.207	0.036	0.735	0.771	0.436	0.052
		31	8300	69.6	1.130	0.021	0.697	0.718	0.412	0.050
		34	8600	72.2	1.075	0.040	0.596	0.636	0.439	0.051
('r	L. A.	.9	5235	58.0	1.149	0.007	0.966	0.973	0.176	0.034
1/5/31		11	5412	58.5	0.874	0.005	0.590	0.595	0.279	0.051
	С. А.	13 15	$\frac{5743}{6050}$	$59.0 \\ 60.2$	$0.875 \\ 0.964$	$0.003 \\ 0.003$	0.541	0.544	0.331	0.058
	V . A.	18	6250	62.0	0.896	0.003	$0.536 \\ 0.491$	$0.539 \\ 0.504$	$0.425 \\ 0.392$	$0.070 \\ 0.051$
		23	6755	64.S	0.955	0.038	0.716	0.504	0.392 $0.204$	0.031
		26	7025	66.0	0.956	0.038	0.546	0.584	0.372	0.053
Ge	L. A.	8	5150	56.0	0.796	0.011	0.506	0.517	0.279	0.054
1/17/31		10	6025	56.8	0.988	0.017	0.641	0.658	0.330	0.056
		12	6690	58.0	0.999	0.027	0.528	0.555	0.444	0.067
	С. А.	16	7675	60.6	1.001	0.043	0.694	0.737	0.264	0.035
		18 20	8190 8400	62.6 $65.0$	$0.928 \\ 0.916$	$0.044 \\ 0.017$	0.571	0.615	0.313	0.038
		22	S600	66.3	0.994	0.017	$0.651 \\ 0.506$	$0.658 \\ 0.545$	$0.238 \\ 0.449$	$0.028 \\ 0.052$
		21	8730	67.5	0.764	0.040	0.464	0.504	0.260	0.032
Kn	L. A.	7	4500	56.5	0.886	0.017	0.750	0.767	0.119	0.026
2/17/31	C. A.	10	5435	57.5	1.017	0.016	0.626	0.642	0.375	0.069
	C. A.	14	6360	59.7	0.957	0.011	0.662	0.673	0.284	0.044
Rs	C. A.	12	5670 5875	$60.0 \\ 61.0$	$0.790 \\ 0.729$	0.020	0.434	0.454	0.336	0.059
3/26/32		14 15	6000	61.2	0.725	$0.017 \\ 0.013$	$0.423 \\ 0.572$	0.440	0.289	0.049
		16	6150	61.8	0.715	0.017	0.508	$0.585 \\ 0.525$	$0.186 \\ 0.190$	$0.031 \\ 0.031$
P-n	C. A.	7	4825	55.0	0.897	0.014	0.466	0.480	0.417	0.088
3/17/33		10	5600	56.3	0.960	0.024	0.471	0.195	0.465	0.083
		13	6175	58.3	0.799	0.050	0.370	0.420	0.379	0.059
		17	7000	61.2	0.915	0.073	0.469	0.542	0.303	0.043
		18	7200	62.7			0.499	0.559	0.341	0.047
1-g	C. A	20	7350° 7800	67.S 68.2	1.000 $1.019$	$0.023 \\ 0.037$	$0.715 \\ 0.674$	0.738	0.262	0.036
3/19/32		23	\$110	68.5	0.914	0.037	0.601	$0.711 \\ 0.647$	$0.308 \\ 0.297$	$0.039 \\ 0.037$
Bn	C. A.	13	7125	64.8	1.142	0.032	0.596	0.928	0.214	0,030
3/4/32	· • • • •	15	7850	65.5	1.016	0.015	0.745	0.763	0 257	0,030
, .,		17	8200	66.5	1.121	0.011	0.773	0.754	0.337	0.041
		19	8430	68.5	1.117	0.017	0.928	0.945	0.172	0.020
		27 29	9460 9825	$\begin{array}{c} 71.3 \\ 71.6 \end{array}$	$\frac{1.125}{1.140}$	$0.035 \\ 0.054$	$0.757 \\ 0.760$	0.822 0.813	0.303	0.031
** -	0.4	14	6300	60.0	1.019	0.018	0.780	0.798	0.327 0.221	0.033
Hr 4/11/32	C. A.	16	6625	61.0	0.960	0.016	0.676	0.692	0.221	0,035 0,040
1/ 11/ 0~		20	8000	66.2	0.900	0.016	0.566	0.582	0.318	0,040
88	L. A	16	6137	62.6	0,933	0.014	0.546	0.560	0.373	0.061
7/1/31	Evap. milk	18	6413	64.0	$0.769 \\ 0.906$	0.013	0.578	0.591	0.178	0.025
		20	6600	65.0		0,017	0.644	0.661	0.244	0.037

†Citrie neid.

II GIVEN MILK MIXTURES ACIDIFIED WITH LACTIC AND CITRIC ACID

											DOMEST.
P		SPHORUS			HORUS	N IN-		XITROGE XCRETIC			ROGEN ENTION
122-	EXC	RETION		RETE	NTION	TAKE	r;	XCHETT	/1/	1,1,1,1	
TAKE -			mom t ?	TOTAL	DED I'C	TOTAL	URINE	FECES	TOTAL	TOTAL.	PER KG.
TOTAL	URINE	FECES GM.	TOTAL GM.	GM.	GM.	GM.	GM.	CZL	GM.	GM.	GM.
GM.	GM.										
0.790	0.528	0.069	0.597	0.193	0.036	3.78	1.86	0.76	2.62	1.16	0.215
0.830	0.408	0.142	0.550	0.280	0.046	4.35	1.97	0.50	2.47	1.88	0.306
0.700	0.398	0.079	0.477	0.223	0.034	3.48	2.77	0.23	3.00	0.48	0.073
0.787	0.420	0.076	0.496	0.291	0.042	4.28	2.46	0.27	2.73	1.55	0.224
0.664	0.397	0.086	0.483	0.181	0.024	3.46	2.45	0.21	2.66	0.80	0.107
0.739	0.428	0.116	0.544	0.195	0.026	3.78	2.98	0.41	3.39	0.49	0.066
0.707	0.406	0.076	0.452	0.225	0.029	3.48	2.50	0.23	2.73	0.75	0.097
1.061	0.561	0.182	0.743	0.318	0.038	4.24	3.51	$0.31 \\ 0.30$	3.82	0.42	$0.051 \\ 0.202$
0.979	0.533	0.134	0.667	0.311	0.038	5.01	3.03		3.33	1.67	
0.935	0.430	0.137	0.567	0.368	0.042	4.80	2.82	0.29	3.11	1.69	0.197
0.851	0.406	0.220	0.626	0.225	0.043	4.30	1.72	0.27	1.99	2.31	0.440
0.646	0.399	0.107	0.506	0.140	0.026	3.20	2.07	0.22	2.29	0.91	0.168
0.652	0.314	0.109	0.423	0.229	0.042	3.08	1.77	0.32	2.09	0.99	0.172
0.771	0.386	0.081	0.467	0.304	0.050	4.30	2.26	0.20	2.46	1.84	0.304
0.735	0.416	0.053	0.469	0.266	0.035	3.85	2.75	0.20	2.95	0.90	0.144
0.825	0.477	0.142	0.619	0.206	0.030	4.46	3.10	0.21	3.31	1.15	0.170
0.770	0.359	0.153	0.512	0.258	0.036	4.05	2.37	0.28	2.65	1.40	0.198
0.632	0.326	0.109	0.435	0.197	0.038	3.12	1.71	0.19	1.90	1.22	0,236
0.766	0.514	0.070	0.584	0.182	0.030	3.69	2.46	0.26	2.72	0.97	0.161
0.765	0.443	0.084	0.527	0.238	0.036	3.85	2.65	0.31	2.96	0.89	0.133
0.784	0.554	0.080	0.634	0.150	0.020	3.16	2.95	0.21	4.04	0.88	0.115
0.816	0.552	0.115	0.667	0.149	0.018	4.20	3.10	0.23	3.33	0.87	0.106
0.772	0.509	0.156	0.665	0.107	0.013	4.17	2,86	0.24	3.10	1.07	0.127
0.781	0.474	0.106	0.580	0.201	0.023	3.81	2.82	0.26	3.08	0.73	0.085
0.615	0.399	0.084	0.483	0.132	0.015	3.30	2.42	0.26	2.68	0.62	0.071
0.687	0.436	0.142	0.578	0.109	0.024	3.61	2.16	0.55	2.71	0.90	0.200
0.777	0.559	0.037	0.596	0.181	0.034	4.08	2,68	0.28	2.96	1.12	0.206
0.728	0.587	0.035	0.622	0.106	0.017	3.81	2.28	0.27	2.55	1.26	0.200
0.566	0.311	0.031	0.342	0.224	0.040	3.20	1.89	0.17	2.06		
0,559	0.325	0.035	0.363	0.224	0.033	2.72	1.88	0.39	2.00	1.14	0.201
0.554	0.343	0.057	0.400	0.154	0.026	2.91	1.96	0.43	2.39	$0.45 \\ 0.52$	0.077
0.537	0,365	0.044	0.409	0.128	0.021	2.89	1.79	0.34	2.33	0.52	$0.087 \\ 0.123$
0.674	0.447	0.018	0,465	0.209							
0.722	0,489	0.014	0.403	0.209	$0.044 \\ 0.039$	$\frac{2.30}{3.51}$	$\frac{1.57}{2.72}$	0.28	1.85	0.45	0.093
0.601	0,394	0.025	0.419	0.218				$0.48 \\ 0.37$	3.20	0.31	0.055
0.628	0.428	0.021	0.469	0.159				0.37	$\frac{2.49}{2.73}$	$0.35 \\ 0.79$	0.054
0.671	0.424	0.026	0.450	0.221				0.38	3.80	0.79	0.113
						_					0.132
0.830 $0.780$	0.560 $0.455$	0.100 0.140	0.660 0.595	0.170 $0.185$				0.48	3,43	1.02	0.139
0.780	0.417	0.127	0.544	0.189		20.7.0		0.46	2.96	1.70	0.218
						•		0.79	3.16	1.11	0.137
0.793	0.575	0,047	0.622					0.46	3.68	0.97	0.136
0.769	0.549	0.057	0.606				2.91	0.43	3.34	0.96	0.123
0,816 0,773	0.516 0.472	0.115 0.096	$0.631 \\ 0.588$					0.59	3.37	0.70	0.085
0.273	0.639	0.092	0.555					~,	3.44	0.69	0.082
0.915	0.633	0.114	0.747						3.07	1.10	0.115
									3.35	0.93	0.095
0.711	0.521	120.0	0,602						3.18	0.87	0.138
0.765 0.734	0,479 0,475		0,532 0,537					0.47	3,19	1.09	0.165
							2,68	0.56	3.24	0.86	0.105
0.759							1.73	0.53	2.26	1.52	0.248
0.702							2,35	0,49	2,84	0.37	0.248
0.751	0,452	0.110	0,601	0.18	0.037	3.83	2.55		3.10	0.70	0.106
											V+100

TABLE

DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGEN BY INFANTS

***************************************					GA IN-		CALCIUM XCRETIO			CIUM NTION
NAME	CURD	AGE	WEIGHT	LENGTH	TAKE		ACIDATO.			
DATE OF BIRTH	MODIFIER	WK.	GM.	CM.	TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.
рикти	MOHITEL	11 17.	G.11.	om.	GM.	GM.	GM.	GM.	GM.	GM.
Ie	R*	10	5840	57.0	0.912	0.018	0.519	0.537	0.375	0.064
3/25/31		12	6340	58.S	0.886	0.025	0.613	0.638	0.248	0.039
0/20/01		14	6S35	61.0	0.933	0.026	0.526	0.552	0.381	0.059
		17	7525	63.0	0.932	0.026	0.703	0.729	0.203	0.027
		19	8000	64.2	1,031	0.031	0.634	0.668	0.363	0.045
S-r	R	9	4790	56.6	0.724	0.013	0.308	0.321	0.403	0.084
4/10/31		11	5530	58.2	0.534	0.015	0.284	0.299	0.235	0.042
47 107 01		16	5860	61.3	0.666	0.018	0.386	0.404	0.262	0.045
McC-y	R	13	5360	60.2	0.939	0.010	0.524	0.534	0.405	0.075
4/25/31		15	5480	61.6	0.893	0.010	0.580	0.590	0.303	0.055
2/ 60/02		24	7220	66.2	0,929	0.026	0.633	0.659	0.270	0.037
		$\frac{3}{26}$	7433	68.0	0.952	0.032	0.641	0.673	0.279	0.037
		28	7655	69.1	0.898	0.018	0.576	0.594	0.304	0.040
		30	7900	69.8	0.971	0.018	0.758	0.778	0.195	0.025
		32	8075	70.6	0.964	0.013	0.673	0.686	0.278	0.034
		35	8400	72.9	1.032	0.026	0.656	0.682	0.351	0.042
S-z	R	15	6798	64.2	0.823	0.023	0.489	0.512	0.311	0.045
6/30/31		17	6943	65.4	0.736	0.019	0.415	0.434	0.302	0.042
,		20	7020	67.0	0.791	0.014	0.594	0.608	0.183	0.026
		22	7400	68.2	0.931	0.013	0.736	0.749	0.180	0.025
		24	7825	69.6	0.876	0.013	0.661	0.674	0.202	0.026
N-n	L. A.†	18	5725	63.6	1,581	0.027	1.263	1.290	0.290	0.051
8/29/31	$\mathbf{R}$	21	7000	66.5	1.138	0.022	0.757	0.799	0.359	0.051
		30	S56S	73.2	1.081	0.037	0.696	0.733	0.348	0.041
Gt 4/14/32	R	14	5510	57.0	0.921	0.007	0.635	0.643	0.279	0.051
D-r	$\mathbf{R}$	19	7300	63.S	0.844	0.023	0.355	0.378	0.466	0.063
2/5/32		$\frac{21}{21}$	7750	64.2	0.882	0.025	0.544	0.569	0.313	0.041
,,		23	8100	65.2	0.902	0.031	0.588	0.619	0.283	0.035
P-n	R	15	7140	63.0	1.152	0.019	0.896	0.915	0.237	0.033
3/1/32		17	7750	63.5	1.000	0.017	0.816	0.833	0.167	0.022
		19	8000	64.2	1.121	0.019	0.871	0.890	0.231	0.029
		20	8025	64.5	1.082	0.013	0.618	0.631	0.451	0.056

<sup>\*</sup>Rennin.

The chemical data of the calcium, phosphorus, and nitrogen balance studies are given in detail in Tables II, III, and IV, for the infants given acid milks, rennin milk, and evaporated milk, respectively. Because the different infants ingested different amounts of milk, and the retentions of nitrogen and minerals depend in large measure upon the intake of these substances, the data obtained have been charted so as to determine the daily retention per kilogram of body weight for a given per kilogram intake. Different symbols have been employed to indicate the type of feeding used in each study. In general, the younger infants ingested the larger amounts of nitrogen and minerals per kilogram of body weight, although there were exceptions to this rule.

III
GIVEN MILK MIXTURES CURDLED WITH PEPSIN-RENNIN FERMENT

P		OSPHORU		PHOSPI		N IN-		ITROGE: CRETIO			OGEN NTION
IN-	E.	XCRETIO:	`	1.1.1.1.	1102	TAKE					
TAKE TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.		URINE	FECES	TOTAL	TOTAL	PER KG.
GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.
			0.510	0.179	0.030	3.76	2.50	0.34	2.84	0.92	0.160
0.689	0.376	0.134	0.310	0.179	0.035	3.51	2.18	0.27	2.45	1.06	0.167
0.645	0.329 0.364	$0.155 \\ 0.103$	0.467	0.283	0.023	3.94	2.19	0.37	2.56	1.38	0.200
0.750		$0.103 \\ 0.224$	0.626	0.164	0.023	4.37	3.85	0.41	3.26	1.11	0.148
0.790	0.402	0.224	0.578	0.104	0.024	4.40	3.23	0.33	3.56	0.84	0.105
0.772	0.418	0.100	0.516	0.194	0.044	3.30	0.20	0.00	0.00	0.01	0.100
0.595	0.269	0.053	0.322	0.273	0.057	3.06	2.09	0.20	2.29	0.77	0.161
0.409	0.232	0.050	0.282	0.127	0.023	2.18	1.57	0.18	1.75	0.43	0.078
0.461	0.243	0.063	0.306	0.165	0.028	2.58	1.79	0.26	2.05	0.53	0.090
0.000	0.001	0.107	0.478	0.225	0.042	3.64	2.32	0.31	2.63	1.01	0.188
0.703	0.371	0.107	0.418	0.199	0.036	3.68	$\frac{2.32}{2.33}$	0.31	$\frac{2.63}{2.61}$	1.07	0.196
0.654	0.361	0.034	0.433	0.199	0.025	4.20	2.81	0.24	3.05	1.15	0.160
0.791	0.437	0.176	0.612	0.226	0.023	4.38	$\frac{2.31}{2.93}$	0.24	3.26	1.12	0.151
0.864	0.455	0.155	0.566	0.220	0.031	4.58	2.48	0.36	2.84	1.12	0.131
0.804	$0.388 \\ 0.429$	0.203	0.632	0.238	0.031	4.42	$\frac{2.46}{2.57}$	0.33	$\frac{2.84}{2.90}$	1.52	0.230
0.846		0.203	0.607		0.027	4.42	$\frac{2.57}{2.77}$	0.35	$\frac{2.90}{3.12}$	1.29	
0.821	$0.429 \\ 0.435$	0.185	0.620	0.214 $0.254$	0.020	4.43	2.81	0.36	$\frac{3.12}{3.17}$	1.29	0.160
0.874	0.433	0.155	0.020	0.254	0.030	4.40	2.01	0.30	3.17	1.20	0.150
0.623	0.320	0.133	0.453	0.183	0.027	3.59	2.42	0.22	2.64	0.95	0.139
0.585	0.283	0.128	0.411	0.174	0.025	2.83	2.28	0.26	2.54	0.29	0.042
0.711	0.359	0.136	0.495	0.216	0.030	3.67	2,64	0.25	2.89	0.78	0.111
0.822	0.447	0.237	0.684	0.138	0.019	4.12	2.85	0.28	3.13	0.99	0.133
0.774	0.430	0.201	0.631	0.143	0.018	4.04	2,69	0.32	3.01	1.03	0.132
1.238	0.648	0.374	1.022	0.216	0.038	6.27	4.28	0.48	4.76	1.51	0.260
0.901	0.513	0.203	0.716	0.185	0.027	5.48	3,34	0.31	3.65		0.260
0.941	0.524	0.163		0.254		4.64	3.14	0.38			0.130
0.702	0.415	0.094	0.509	0.193	0.035	4.19	2,63	0.43	3.06	1.13	0.204
0.000	0 215	0.050	0.204	0.055	0.005	0.00	0.00				
0.629	0.315	0.059				2.62	2.28	0.24			0.151
$0.734 \\ 0.727$	0.434	0.115				4.07	2.56	0.58			0.146
	0.427	0.135	0.562	0.165	0.020	4.72	2.45	0.49	2.94	1.18	0.146
0.806	0.517	0.115				4.63	3.18	0.42		1.03	0.145
0.741	0.525					4.23		0.42			0.098
0.769						4.27	2,75	0.29		1.23	0.154
0.740	0.341	0.103	0.444	0.296	0.037	4.17	2.34	0.48			0.156

# NITROGEN

In Chart 3, the retentions of nitrogen per kilogram per day have been plotted against the daily per kilogram intakes of this element, using a different symbol to represent the retention from each type of feeding given. Each symbol represents one period of study of one infant. It is evident from the chart that the quantity of nitrogen retained tends to increase steadily with increasing intake of this element. It seems evident, also, that the range of retention for any given intake of nitrogen is practically identical for all of the milk modifications studied. No one method of preparation proved definitely superior to any other as regards nitrogen retention. It thus appears that when

DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGE:

TABL

NAME DATE OF			LENGTH	CA IN- TAKE		CALCIUM EXCRETIO			CIUM NTION
вікти	WK.	GM.	CM.	TOTAL GM.	URINE GM.	FECES GM.	TOTAL GM.	GM.	PER KG GM.
11—1	10	5130	58.0	0.641	0.002	0.456	0.458	0.183	0.036
8/16/30	12	5470	60.0	0.644	0.004	0.480	0.484	0.160	0.029
	14	6055	62.0	0.999	0.004	0.935	0.939	0.060	0.010
	19	6705	65.2	0.911	0.010	0.571	0.581	0.330	0.049
	21	6775	65.5	1.011	0.001	0.703	0.704	0.307	0.045
	23	7365	66.3	1.179	0.008	0.753	0.761	0.418	0.057
	25	7985	68.0	1.195	0.009	0.763	0.772	0.423	0.053
	27	8125	68.6	1.135	0.007	0.712	0.719	0.416	0.052
	29	7987	69.0	1.130	0.007	0.749	0.756	0.374	0.047
Iz	27	9250	70.8	1.139	0.026	0.807	0.833	0.306	0.033
5/2/30	29	9790	71.5	1.310	0.036	0.906	0.942	0.368	0.038
	34	10113	74.6	1.160	0.017	0.827	0.844	0.316	0.031
	38	10410	76.0	1.205	0.007	0.794	0.801	0.404	0.039
	40	11015	76.3	1.379	0.034	0.884	0.918	0.461	0.042
	43	11200	77.2	1.354	0.032	0.830	0.862	0.492	0.044
	45	11400	78.0	1.297	0.027	0.844	0.871	0.426	0.037
II—n	25	8705	68.8	1.089	0.050	0.723	0.773	0.316	0.036
5/20/30	37	9295	73.5	0.980	0.032	0.684	0.716	0.264	0.028
	39	9675	74.5	1.269	0.055	0.693	0.748	0.521	0.054
	41	9613	75.2	1.342	0.048	0.865	0.913	0.429	0.045
	43	9237	75.7	1.068	0.052	0.414	0.466	0.602	0.065
Ме	26	8050	68.2	1.202	0.014	0.680	0.694	0.508	0.063
5/26/30	39	8545	74.4	1.360	0.030	1.055	1.085	0.275	0.029
-,,	42	9775	75.4	1.208	0.025	0.807	0.932	0.276	0.028

the total caloric intake is high and the milk feeding is so treated as to permit the formation of a fine curd in the infant's stomach, the quantity of nitrogen retained by an infant will vary directly with the quantity of intake of this element.

#### CALCIUM

Chart 4 compares the per kilogram intakes and retentions of calcium for the four groups of infants. The heavy line represents the average retention of calcium as determined from approximately 300 separate studies of infants given acidified whole milk feedings and 350 U.S.P. units of D as cod liver oil daily. It will be observed that the general trend of retention in the present study is similar to that of the larger control group, and the symbols representing retentions during the individual periods of study are about equally distributed on both sides of the average line. The range of calcium retention for any given intake is approximately the same for all of the different types of feedings. It appears, then, that organic acid added to evaporated or finely curded whole milk feedings does not result in any noteworthy increase in the amount of calcium retained by the infant.

IV
BY INPANTS GIVEN UNACIDIFIED EVAPORATED MILK MIXTURES

P IN- TAKE		OSPHORU XCRETION			'HORUS NTION	N IN- TAKE		TTROGE.			ROGEN
TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.	TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.
GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	G71.	GM.	GM.
0.492	0.248	0.116	0.364	0.128	0.025	2.47	1.38	0.38	1.76	0.71	0.138
0.485	0.254	0.109	0.363	0.122	0.022	2.72	1.62	0.33	1.95	0.77	0.141
0.784	0.391	0.278	0.669	0.115	0.019	3.99	2.46	0.66	3.12	0.87	0.143
0.787	0.359	0.195	0.584	0.203	0.030	3.80	2.28	9.63	2.91	0.89	0.132
0.871	0.280	0.288	0.568	0.303	0.045	3.99	2.08	0.73	2.81	1.18	0.174
0.971	0.450	0.224	0.674	0.297	0.040	4.72	2.83	0.51	3.34	1.38	0.188
0.972	0.439	0.221	0.660	0.312	0.039	4.82	2.80	0.55	3.35	1.47	0.185
0.930	0.420	0.205	0.633	9.297	0.037	4.72	2.42	0.49	2.89	1.83	0.225
0.883	0.394	0.181	0.575	0.308	0.029	4.29	2.66	0.48	3.14	1.15	0.144
0.945	0.473	0.281	0.754	0.191	0.020	4.99	3.51	0.74	4.25	0.74	0.081
1.085	0.485	0.311	0.776	0.289	0.030	5.45	3.34	0.85	4.19	1.26	0.129
0.985	0,506	0.293	0.799	0.186	0.018	4.75	3.56	0.48	4.04	0.71	0.070
0.976	0.525	0.290	0.815	0.174	0.017	5.02	3.39	0.49	3.88	1.14	0.110
1.112	0.509	0.283	0.792	0.320	0.029	5.34	3.65	0.62	4.67	0.67	0.061
1.111	0.545	0.269	0.814	0.297	0.027	5.23	3.72	0.58	4.30	0.93	0.088
1.075	0.554	0.276	0.830	0.245	0.022	5.03	3.88	0.57	4.4.5	0.58	0.051
0.005	0.470	0.074									
0.937	0.412	0.254	0.666	0.271	0.031	4.77	2.99	0.57	3.56	1.21	0.139
0.814	0.414	0.208	0.622	0.192	0.020	4.31	2.81	0.51	3.32	0.99	0.107
1.004	0.522	0.179	0.701	0.303	0.031	4.90	3.17	0.42	3.59	1.31	0.136
1.051	0.414	0.236	0.650	0.404	0.042	5.20	2.30	0.60	2.90	2.32	0.238
0.882	0.375	0.129	0.504	0.378	0.041	4.28	2.62	0.28	2.90	1.38	0.150
1.025	0.466	0.269	0.505	0.000	0.000	* ^-					
1.025	0.400 $0.331$	0.269 $0.385$	0.735	0.290	0.036	5.23	3.54	0.68	4.22	1.01	0.126
0,931	0.331 $0.374$	0.383 $0.279$	0.716	0.380	0.038	5.33	2.90	0.76	3.66	1.67	0.175
	0.014	0.219	0.653	0.254	0.029	4.66	2.72	0.56	3.28	1.38	0.141

# PHOSPHORUS

As phosphorus is used both for bone and for soft tissue formation, the quantity of phosphorus retained by an infant will depend very largely upon the calcium and nitrogen retentions. The retentions of both of these elements were apparently unaffected by the various methods of preparation of feedings used. It was therefore to be expected that the phosphorus retentions likewise would be unaffected. Chart 5 shows that the daily per kilogram retention of phosphorus is increased with increasing intakes of this element, but that the range of retention for any given intake is the same whether the milk used was evaporated or curded with rennin or with acid.

# SUMMARY AND CONCLUSIONS

This paper reports 108 balance studies in which were determined the retentions of nitrogen, calcium, and phosphorus by infants fed curded whole milk or evaporated milk mixtures, with 6 per cent carbohydrate additions. The quantity of vitamin D administered daily was constant throughout the experiment. In most instances the studies were continued over a sufficient period to determine the effect of the feeding

upon the growth and development of the infant. Ten infants were given whole or evaporated milk feedings acidified with lactic or citric acid: for eight infants the milk was curded by the addition of a pepsinrennin preparation; and four infants were fed unacidified evaporated milk mixtures. All of the above milk mixtures have in common the property of permitting a fine curd in the infant's stomach.

- 1. The growth of each infant, both in length and weight, was somewhat above the average rate.
- 2. Roentgenograms of the wrist and ankle, taken at regular intervals, showed normal development and calcification of bone.
- 3. The retentions of the three elements studied, nitrogen, calcium, and phosphorus, all increased steadily with increasing intake. amount of variation in retention at each intake level was approximately the same for each of the milk mixtures studied.

It is therefore concluded that if curded whole milk, or uncurded evaporated milk mixtures are fed to infants, the amounts of nitrogen and minerals available for absorption and retention are the same for any given intake of milk, whether the milk is curded by the addition of acid, by enzymes, or is altered by the long heat treatment of evaporation so that the curd formed in the stomach is small. The excellent growth and bone development, as well as the high retentions of the elements studied, constitute evidence that all of these milk mixtures are good foods for infants.

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# THE RETENTIONS OF NITROGEN, CALCIUM, AND PHOSPHORUS OF INFANTS FED SWEETENED CONDENSED MILK

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THE minimal protein requirement of infants has never been actually determined. It has been generally assumed, however, that infants fed cow's milk require a considerably greater intake of protein than do breast-fed infants. A nursing infant receives about 8 per cent of his total calories in protein, whereas an artificially fed infant is said to require at least 12 per cent of his calories in protein. This difference in protein requirement is explained by the higher lactalbumin content of human milk since Osborne and Mendel demonstrated that less lactalbumin than easein was necessary to maintain normal growth in the rat. Edelstein and Langstein attempted to prove that these findings were valid also for the human infant, but owing to the inherent difficulties of the method employed, their results were not entirely conclusive. No other similar experiments have been reported.

Although experimental evidence is lacking, most writers on infant nutrition attribute the nutritional disturbances occasionally seen in infants fed cow's milk mixtures providing less than 12 to 15 per cent of the calories in protein to deficiency of protein. Sweetened condensed milk which contains about 10 per cent of its calories in protein is frequently cited as an example of a feeding inadequate in protein. It is well known, however, that many modifications of cow's milk designed to resemble human milk, and consequently low in protein, are used for infant feeding without any evidences of impaired nutrition.

The nitrogen balances of infants fed a cow's milk mixture low in protein should afford an indication of the adequacy of the intake of protein. The present study was, therefore, undertaken to determine the retention of nitrogen of infants fed a cow's milk mixture providing about 10 per cent of the calories in protein. Sweetened condensed milk was used, but the results probably apply to other cow's milk modifications of similar protein content.

#### METHOD

The subjects of the experiments were five healthy infants ranging from four to seven months of age. Their nitrogen balances were determined first when given diluted sweetened condensed milk and then

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when fed an equal number of ealories in the form of a cow's milk mixture providing about 15 per cent of the calories in protein. This consisted of unsweetened evaporated milk diluted with an equal volume of water to which was added sucrose to make up 6 per cent by weight of the total mixture. In addition, one infant was studied during a third period on a feeding of diluted evaporated milk without added sugar which supplied 20 per cent of the calories in protein. The percentage of distribution of calories of the feeding mixtures used is shown in Table I. Both the sweetened condensed milk and the evaporated milk mixtures were supplemented with 8 c.c. of cod liver oil and 30 c.c. of orange juice daily. The total calories fed were sufficient to allow normal gain of weight and ranged from 100 to 120 calories per kilogram. Since sweetened condensed milk mixtures are relatively low in calcium and phosphorus, the retentions of these elements were also determined in addition to the retention of nitrogen.

Each infant was fed the milk mixture to be studied for at least ten days before the balance determinations. Following this foreperiod, the infants were placed on metabolism frames permitting the quantitative collection of urine and feces. The metabolism periods were of seven

TABLE I
PERCENTAGE DISTRIBUTION OF CALORIES

I	PROTFIN	FAT	CARBOHYDRATE
Sweetened condensed milk	10	25	65
Evaporated milk and 6 per cent sucrose	15	40	4.5
Evaporated milk	20	55	25
Breast milk	8	47	45

days each. Carmine red was used to mark the feces. Aliquots of the milk mixture fed were taken for analysis. The food, feces, and urine were analyzed for nitrogen by the Kjeldahl method, calcium by a modification of the McCrudden method, and phosphorus by the gravimetric magnesium pyrophosphate method. The accuracy of the urine collections was checked by the determination of creatinine in each twenty-four-hour specimen. During each period the variations in the daily creatinine exerction were less than 10 per cent of the average for the period. The gain in weight of the infants was also noted.

## RESULTS

The experimental results are summarized in Table II. The data are expressed in terms of twenty-four-hour periods.

The rate of gain in weight was satisfactory in all of the experiments, ranging from 19 to 41 gm. per day, and was essentially the same during the periods of feeding with sweetened condensed milk and with evaporated milk.

In four of the five experiments the retentions of nitrogen during the periods of low protein feeding were approximately equal to the retentions obtained with the higher levels of protein. The constancy of retention of nitrogen is quite strikingly shown by the subject E. M., who retained the same amount of nitrogen when 10 per cent, 15 per cent or 20 per cent of the calories were provided in protein. One subject, H. B., showed a considerably greater retention of nitrogen during the evaporated milk period.

The sweetened condensed milk feedings supplied only about twothirds as much calcium and phosphorus as the mixtures of evaporated milk and sucrose. Less calcium was retained during the periods of lower calcium intake except in one experiment. The retentions of phosphorus corresponded approximately to those expected from the calcium and nitrogen balances, i.e.,

P retention = 
$$\frac{\text{Ca retention}}{2} + \frac{\text{N retention}^5}{17.4}$$

TABLE II

DAILY NITROGEN, CALCIUM, AND PHOSPHORUS BALANCES

st'B	AGE	WEIGHT	FEED-	WT.	N	N	GV.	CA	P	P
		GM.	120	CMN	INT.	RET.	INT.	RET.	INT.	RET.
JECT	110.	Gu.	120	GM.	GM.	GM.	GM.	GM.	GM.	GM.
W.K.	5	7,655	C.M *	+35	2.92	+1.19	0.67	+0.22	0.55	+0.18
		9,600	E.M. 18.1	+36	4.46	+1.22	1.04	+0.33	0.82	+0.24
H. B.	7	7,915	C.M.	+39	2.65	+0.64	0.64	+0.24	0.52	+0.10
		8,670	E.M.+8.	+36	4.47	+1.12	1.04	+0.16	0.83	+0.17
т. в.	6	7,915	C.M.	+11	2.55	+0.96	0.57	+0.23	0.47	+0.17
		8,660	E.M.+S.	+40	4.38	+0.87	1.05	+0.32	0.79	+0.10
т. т.	5	7,260	C.M.	+23	2,60	+0.82	0.58	+0.17	0.47	+0.14
		7,720	E.M.+8.	+39	4.38	+0.82	1.05	+0.21	0.79	+0.1
Е. М.	4	6,025	С.М.	+35	2,40	+0.82	0.56	+0.17	0.42	+0.1
		6,765	E.M.+8,	+19	4.02	+0.83	1.06	+0.20	0.73	+0.1
		7,455	E.M.;	129	5.63	+0.80	1.37	+0.24	1.02	+0.1

<sup>\*</sup>C M., diluted sweetened condensed milk.

# DISCUSSION

The failure of four of the subjects to show increased retention of nitrogen when the protein calories were increased from 10 to 15 per cent of the total calories indicates that the lower level of protein was sufficient to permit the maximum possible protein storage. The one subject, H. B., who showed less retention of nitrogen during the sweetened condensed milk period may not have been adjusted to the low protein feeding at the time the collection of urine and feces was started, since he showed increasing daily retentions of nitrogen during the period of low protein feeding. However, if this lower retention of 0.64 gm.

<sup>†</sup>EM + S, diluted evaporated milk with 6 per cent sucrose,

IDM., diluted evaporated milk without added sucrose,

nitrogen daily be accepted, it still compares favorably with the reported retention of nitrogen of breast-fed infants. According to the literature, the daily nitrogen balance of healthy infants fed human milk averaged 0.56 gm.6 Swanson7 determined the retention of nitrogen of an infant fed human milk for a period of almost six months and found the average daily retention to be 0.54 gm. When sufficient calories are given, cow's milk mixtures which provide 10 per cent of the calories in protein apparently satisfy the infant's protein requirements. Increasing the protein in the diet above this level without increasing the calories does not result in increased storage of protein. The greater retention of nitrogen of artificially fed infants as compared with breast-fed infants, and especially of infants fed concentrated milk mixtures, may be associated with a higher intake of calories rather than of protein. Nelson<sup>8</sup> and Jeans and Stearns found that the retentions of nitrogen of infants fed undiluted milk or evaporated milk mixtures were greater than those of infants fed diluted milk mixtures. The infants receiving the concentrated mixtures were given more calories as well as more protein than the infants receiving the diluted milk feedings.

No conclusions as to the protein minimum, meaning by this term, the lowest level of dietary protein permitting the maximum retention of protein, can be drawn from the present experiments. The fact that one subject showed a relatively low retention of nitrogen when given the 10 per cent protein feeding may indicate that this level is close to the minimum for infants fed cow's milk.

The nitrogen balances of the infants given sweetened condensed milk feedings do not support the commonly expressed belief that sweetened condensed milk is an inadequate food for infants because of its low content of protein. It is possible that the poor results of sweetened condensed milk feedings may have been due to deficiency of vitamins rather than of protein. This is in accord with the findings of De Sanctis and Craig¹o and Wolf and Sherwin¹¹ who reported normal growth and development in infants fed sweetened condensed milk supplemented with additional sources of vitamins C and D.

The lower intake of calcium and phosphorus during the periods of feeding with sweetened condensed milk was apparently associated with smaller retentions of these elements. This should not necessarily be interpreted as signifying that sweetened condensed milk is inadequate with respect to calcium and phosphorus. It has been observed many times that infants fed cow's milk supplemented with vitamin D show much greater retentions of calcium and phosphorus than do breast-fed infants. This is true even when the balance studies are carried out for long periods of time.<sup>7, 12, 13, 14</sup> Swanson<sup>7</sup> over a period of three months found that the daily retention of calcium of an infant fed human milk supplemented with cod liver oil averaged 0.08 gm. daily, whereas that of an infant fed a cow's milk mixture plus cod liver oil averaged 0.29 gm.

daily. Neither of these infants showed any evidences of rickets. Greater retentions of calcium and phosphorus can be obtained in infancy by increasing the amount of these elements in the diet, as the studies of Nelson15 and Jeans and Stearns9 show, but there is no evidence that this increased retention of calcium and phosphorus is necessary. Although the retentions of calcium and phosphorus of infants fed sweetened condensed milk supplemented with cod liver oil are less than those obtained with higher intakes of calcium and phosphorus, they are, nevertheless. considerably greater than those reported in normally growing breast-fed infants and are probably adequate.

#### STIMMARY

The retentions of nitrogen, calcium, and phosphorus of five infants ranging from four to seven months of age were determined when fed cow's milk mixtures providing 10, 15, and in one case 20 per cent of the calories in protein. The 10 per cent protein feeding consisted of diluted sweetened condensed milk. The feedings were all supplemented with orange juice and cod liver oil.

With an adequate intake of calories, the protein requirements of the infants were apparently satisfied when 10 per cent of the calories were provided by protein.

The retentions of calcium and phosphorus of infants fed sweetened condensed milk supplemented with cod liver oil were less than the retentions observed when the amounts of calcium and phosphorus in the diet were increased but were, nevertheless, considered sufficient to permit normal growth.

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# RESPIRATORY FAILURE IN ACUTE EPIDEMIC POLIONYELITIS

# LATE RESULTS AND COMPLICATIONS

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IN A PREVIOUS communication we reported in detail our observations in forty-six patients with poliomyelitis treated in the Drinker respirators at the Willard Parker Hospital in 1931. We now present the follow-up data of these patients obtained over a period of four years after respirator treatment. During 1932 and 1933 seventeen additional patients with poliomyelitis were treated in the respirators at the Willard Parker Hospital. We shall summarize our observations in the entire group of sixty-three patients and discuss a frequent late pulmonary complication which often is not recognized.

# ANALYSIS OF SIXTY-THREE CASES

Types of Patients Treated.—The patients were divided into two groups (spinal and bulbar), according to the type of respiratory paralysis present. The patients in the first group had paralysis of the diaphragm or the intercostal muscles\* or both and were classified as spinal cases. Paralysis of the intercostal muscles was determined by watching the expansion of the chest during inspiration. The magnitude of expansion was more readily estimated by pressing firmly on the upper abdomen, thus diminishing the excursion of the diaphragm. Paralysis of the diaphragm was determined by observing the movement of the abdominal wall during inspiration. If there was no abdominal movement, or if the abdomen was drawn inward during inspiration, it indicated weakness or paralysis of the diaphragm. The involvement of the respiratory muscles was often unilateral. Fluoroscopy was sometimes used to corroborate the clinical impression.

The patients in the second group had involvement of the cranial nerves with apparent injury of the respiratory center and were classified as having bulbar lesions.† The diagnosis of injury to the respiratory center was made in patients with bulbar lesions, whose respirations were irregular in depth and rate at a time when the upper air passages

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<sup>\*</sup>The diaphragm and intercostal muscles are not the only ones that function during inspiration. Some of the other muscles are the levators costarum, scaleni, sternocleido-mustold, pectoralis minor and serratus posticus superior. These may also be paralyzed but are of minor importance.

<sup>†</sup>Bulbar is used in the broad sense. Although it is anatomically incorrect, it has become accepted usage to divide the more common lesions in poliomyelitis into spinal and bulbar. The latter includes the nuclei of the cranial nerves as well as the respiratory center.

were not obstructed (by mucus or saliva), and who did not have paralysis of the respiratory muscles.

There were several patients with paralysis of the intercostal muscles or diaphragm who also had paralysis of some cranial nerves. These patients were considered as having spinal lesions, so far as the respiratory paralysis was concerned. Similarly some patients with involvement of the respiratory center had paralysis of one or more extremities, but, so far as the respiratory paralysis was concerned, they were considered as having bulbar lesions.

When determining injury to the respiratory center, it is important to have the upper air passages free of mucus and saliva. An erroneous diagnosis of respiratory paralysis was made in at least two patients who were unable to swallow. The mucus and saliva which accumulated in the pharynx of these patients interfered with respiration. Each one received respirator treatment for several hours without improvement. After removal from the respirator and the institution of suitable treatment, they improved and finally made a complete recovery. Placing such patients in the respirator is likely to result in emphysema and aspiration pneumonia as Harper and Tennant<sup>2</sup> have pointed out. These patients are not included in the sixty-three cases under consideration in this paper.

Age and Sex.—The voungest patient treated was fourteen months of age and the oldest twenty-four years. There were four patients under three years of age, all of whom died. The distribution between the sexes showed nothing significant.

Time Factors.—There was apparently no correlation between the duration of the respiratory difficulty and the ultimate result. Some patients who were placed in the respirator shortly after the appearance of respiratory embarrassment died; whereas others, who had respiratory embarrassment for as long as nine days before treatment survived.

Differential Diagnosis.—Pneumonia, asthma, and other conditions are not infrequently erroneously diagnosed as respiratory paralysis due to poliomyclitis, and patients with these conditions are sent to the hospital for treatment. Gordon<sup>3</sup> found that seventeen cases of pneumonia were incorrectly diagnosed as poliomyclitis and sent to the Herman Kiefer Hospital during a time when the total number of patients admitted with poliomyclitis was 224. In 1933 nine patients with pneumonia were sent to the Willard Parker Hospital for treatment.<sup>4</sup> Probably many such errors in diagnosis could be avoided by obtaining a careful history and performing a thorough physical examination. We have never seen a patient with involvement of the respiratory muscles due to poliomyclitis who did not have, in addition, paralysis or paresis of some other muscles.

Pulmonary Complications.—Twenty-seven of the sixty-three patients treated in the respirators were discharged from the hospital. Twelve

TABLE I
ANALYSIS OF TWELVE DEATHS AFTER RESPIRATOR TREATMENT

	TIME IN- TERVAL		
CASE NO.	BETWEEN		
	END OF		
HOSPITAL	PIRATOR	DODY, CONTOOD 171	TERMINAL ILLNESS, CLINICAL DIAGNOSIS,
NO.	TREAT-	ROENTGENOGRAM	AND COURSE
AGE	MENT	}	
	AND		
	DEATH		
1	8 mo.	Massive atelectasis	Seven months after discharge patient had
4311			scarlet fever and varicella. During con-
5 yr.			valescence temperature rose, and patient
			became dyspneic. Clinical diagnosis of
			pneumonia was made. During next eight days patient became progressively worse
	1	}	and died. First roentgenogram showed
			atelectasis which was later complicated
		[	by a bilateral pneumonia.
2	3 wk.	Massive atelectasis	Normal convalescence at an orthopedic hos-
4325			pital for 9 days; patient developed upper
3 yr.			respiratory infection for 2 days and then suddenly became desperately ill with
	}		dyspnea and cyanosis. Clinical diagnosis
			was pneumonia, but roentgenogram
	}		showed a massive atelectasis of entire
			right lung. Patient died 20 hr. after onset of acute symptoms.
3	2 yr.	Six months before	Patient had anorexia, cough, and fever at
4751	ļ	fatal illness pa-	home for one week. Cough became worse,
13 yr.		tient had massive atelectasis from	and patient vomited. Hoarseness and dyspnea developed. Examination at hos-
		which he recov-	pital revealed coarse moist râles in both
		ered.	lungs, diminished resonance and fremitus,
		}	and profuse nasal discharge. Temperature 101.4° F. The same night he be-
			came restless and cyanotic; pulse was
	}		feeble. Few hours later he was uncon-
	1		scious. He died 16 hr. after admission.
			Diagnosis was cardiovascular failure, pneumonia, and possibly pulmonary
	\		edema.
4 4925	6 wk.		Patient was doing well at an orthopedic
6 yr.	72 31.		hospital for one month. Suddenly pa- tient developed respiratory difficulty with
-	1		cough and slight cyanosis. Moist râles
	}	}	were heard over entire chest. Temper-
	1		ature 100° F. Diagnosis of bronchial
	{		pneumonia was made. Respirator treat- ment and oxygen did not help. The fol-
	1		lowing days the temperature was between
			103 and 104° F. Condition became
	1		worse, and patient died five days after
5	21/2 yr.		onset of acute symptoms.  Convalescence had been progressive. He
4323			developed a slight cold with cough, sim-
11 yr.	}		ilar to condition he had on previous oc-
			casions. This time there was a more copious secretion of mucus. Temperature
			was normal. Suddenly he became dysp-
			neic, evanotic, and apprehensive. Coarse
			moist rales in both lungs, more at the
			apices, no dullness. Impression was pul- monary edema. He died 10 hr. after
		}	onset of acute symptoms.

TABLE I-CONT'D

		***************************************	
	TIME IN-		
	TERVAL		
CASE NO.	BETWEEN		
	ENDOF		
HOSPITAL	OUR RES-		TERMINAL ILLNESS, CLINICAL DIAGNOSIS,
NO.	PIRATOR	ROENTGENOGRAM	AND COURSE
	TREAT-		
AGE	MENT		_
	AND		
	DEATH		
6	3½ mo.		Uneventful convalescence at Willard Parker
4719	0 /2 110.		Hospital for 3 weeks and another hospi-
11 yr.			tal for 9 months. Warmanature 0091-
7	{		tal for 2 months. Temperature 99° to
			100° F., pulse 90 to 100, and respira-
			tions 20 to 26. Taken home against ad-
	1		vice of attending physicians. Apparently
	1		well at home for 3 weeks. Then sud-
	}		denly patient became ill, complained of
			headache, rapidly became stuporous, and
			developed difficulty in breathing and cy-
			anosis. Three hours after onset admitted
	}		to Fordham Hospital as an emergency case. Impression was preumonia and
			possibly relapse of poliomyelitis. Placed
			in respirator with some improvement in
			color. Stupor persisted, pulse poor, temperature 100° to 102° F. Patient died
			25 hr. after admission. Unfortunately
	!		25 hr. after admission. Unfortunately the case record and autopsy report could
			not be found.
7	3 wk.		
5776			Patient discharged in satisfactory condition
14 yr.	1		after 10 days in general hospital. The day the patient arrived home there was
•			a sudden enset of dramer and
			a sudden onset of dyspnea and cyanosis with rapid development of coma. There
	1 1		were distant breath sounds over both
	1		ture 103° F. In respirator 10 hr. with-
	{		out improvement; died 20 hr. after onset
			of acute symptoms.
8	2 wk.		This patient was discharged from Willard
4669	1		Parker Hospital to another hospital for
5 yr.			further respirator treatment in order to
		į	make room for more urgent cases. He
	1		was treated for 5 days more with im-
			provement and removed from the respi-
			I work the pattern was taken been t
	-		the parents against the advice of his
			t to the time, tilling the total total
	1		
	1		
	1		
	1		
		}	There was some improvement, but after
		}	
	1		dyspnea, cyanosis, and restlessness de-
	}	i	
	1	1	He died 10 minutes after recurrence of acute symptoms
9	11/2 yr.		
5511	1		Letter from mother states patient died of
13 yr.	1		pneumonia at home.
		·	<u> </u>

TABLE I-CONT'D

CASE NO	TIME IN TERVAL BITWEEN		(
HOSPITAI NO AGE	OUR PES PHATOL THAT MENT	LOFNICFNOGAM	IERMINAL ILINESS, CLINICAL DIAGNOSIS, AND COURSE
10	DEATH		
10 7523 15 yr	5 mo		Letter from mother states patient died of pneumonia at home after an illness of 4 days Ovygen administered without benefit.
11 5300 10 yr	21/2 31		Letter from mother states that patient died of pneumonia at home in Lenox, Mass, 24 hours after onset of acute symptoms.
12 5114 20 yr	6 mo		Patient had been convalescing nicely for 6 mo. at a general hospital Died of agran ulocytosis after administration of several doses of anudopyrine for abdominal pain

of these twenty-seven patients who survived the respirator treatment in the hospital died at intervals of from two weeks\* to two and one-half years afterward. The cause of death in these twelve patients is of considerable interest. All of them had residual paralysis of some of the respiratory muscles. One patient developed neutropenia following the administration of amidopyrine for several days. The fatal illness in the other eleven patients began with respiratory symptoms, and the clinical diagnosis in eight was pneumonia and in one, pulmonary edema. Roentgenograms were taken of the two remaining patients during their final illness, and in both a roentgenologic diagnosis of massive atelectasis was made. The clinical diagnosis in these two patients was pneumonia (Table I, Cases 1 and 2)

It is sometimes most difficult to differentiate clinically between massive atelectasis and pneumonia, even when one keeps in mind that either condition may be present. Although pneumonia may develop after respirator treatment, it is significant that in none of the patients in whom pneumonia was the final diagnosis was this confirmed by roentgenograms. We were able to obtain a fairly accurate description of the fatal illness in a few instances, and some of these closely simulated the sequence of events in cases of massive atelectasis (Table I, Cases 3 to 6). There was a history of an upper respiratory infection in some, with moderate ineffectual cough and rapidly progressing dyspnea. Cyanosis developed despite treatment in a respirator or the administration of oxygen by nasal catheter. There was usually a rise in temperature which varied from 2° to 6° Fahrenheit. The respiratory excursion was diminished on the affected side (sometimes obscured by the muscle paralysis),

<sup>&</sup>quot;The potient who died offer two weeks was removed from the hospital against the advice of the attending physicians,

and suppressed breath sounds with moist râles were heard over the involved area. The condition became progressively worse, and death occurred in from a few hours to several days.

Although massive atelectasis was a serious occurrence in our handicapped patients, it developed in some of them during, as well as after, respirator treatment without a fatal issue. Two patients had atelectasis of the right upper lobe while in the respirator. The diagnosis was made clinically and confirmed by roentgenograms. Three other patients developed massive atelectasis two weeks, four months, and two years after their treatment in the respirator and recovered.

Massive atelectasis is the result of a prolonged occlusion of the lumen of a large bronchus. Several factors were present in our patients which predisposed them to such an occurrence. There was an intercurrent upper respiratory infection which increased the production of mucus. All the patients were able to cough but with diminished force, because some of the respiratory muscles were still paralyzed. We believe that the ineffectual cough permitted mucus to accumulate in the tracheobronchial tree which, in some instances, was followed by the plugging of a bronchus. The air in the alveoli related to that bronchus was absorbed, and the result was massive atelectasis.

Pathology.—We shall consider briefly the pathologic conditions found in the lungs of patients who died during treatment in the respirator. Most of the pathologic material was examined by Dr. Lawrence W. Smith at the Willard Parker Hospital. Emphysema and focal areas of atelectasis (lobular) were found in all cases. A few patients not treated in the respirator showed atelectasis and emphysema but not to the same extent. Vascular engorgement, congestion, stretching of the elastic tissue fibers, and an alveolar exudate of serum and blood cells were frequently found in treated cases. When the ehest was opened in one case, the lungs were partially collapsed due to a loss of the normal elasticity. Similar findings have been reported by others.<sup>2-5</sup>

Patients Suitable for Treatment in the Respirator.—Should every patient with poliomyelitis who experiences difficulty in breathing receive respirator treatment? Because this question is of great importance we shall discuss it in detail and state why our answer is in the negative. Respiratory difficulty in poliomyelitis may be caused by (1) paralysis of the respiratory center, (2) paralysis of the diaphragm or intercostal muscles, either separately or in combination, or (3) accumulation of saliva and mucus in the retropharynx in patients with inability to swallow.

We have not been successful in the treatment of patients having bulbar lesions with paralysis of the respiratory center. Discouraging results with similar cases have been reported by other authors.<sup>2, 8</sup> Whether

these patients die of respiratory paralysis, cardiovascular failure, toxemia, or some other condition is not clear. Possibly more of them would survive if the respirator was not used.

Patients with inability to swallow accumulate mucus and saliva in the retropharynx which may interfere with respiration. Aspiration of oral secretions or vomitus during normal or artificial respiration is a constant danger and may lead to atcleetasis, emphysema, or pneumonia. If there is no respiratory paralysis, the patients will be able to breathe provided that the air passages are kept clear. Postural drainage, frequent use of a suction apparatus, parenteral administration of fluids, and no oral feeding for several days is the regime we have used for such patients.<sup>9</sup>

The most frequent cause of respiratory embarrassment in patients with poliomyelitis is due to spinal lesions which result in paralysis of the diaphragm or intercostal muscles. It is in this group that one finds patients suitable for respirator treatment. For patients with paralysis of one side of the diaphragm, or only some of the intercostal muscles, who do not have eyanosis or dyspnea, we do not advise respirator treatment. On the other hand, it has been suggested that the respirator should be used at the first sign of involvement of the respiratory muscles, in order to rest the injured nerve cells. Unfortunately, at present, we do not know whether artificial respiration prevents stimulation of the nerve cells associated with respiration. The conditions produced by artificial respiration are not comparable to the immobilization of the paralyzed skeletal muscles of an extremity. A further analogy to skeletal muscles which is sometimes made does not necessarily apply to the respiratory muscles. The impression is that spontaneous breathing will stretch the weakened respiratory muscles, just as weakened skeletal muscles of an extremity are stretched by incorrect immobilization or during active motion by antagonistic muscles. There are functionally no antagonistic muscles to the diaphragm or intercostal muscles, and therefore stretching of the paralyzed muscles will not occur. Another point to be borne in mind is that pulmonary complications may occur in patients treated in the respirator. We have observed many patients with respiratory embarrassment due to poliomyelitis who were not treated with artificial respiration. As far as we know, none of these developed pulmonary complications similar to those described earlier in this paper. For these reasons a patient should be in a respirator only if he is unusually restless, fatigued, or dyspneic or has eyanosis which cannot be relieved by the administration of oxygen. For patients with slight or moderate respiratory distress we advise repeated small doses of sedatives and continued reassurance to make them more comfortable and enable them to rest.

Treatment.—We have described the care of the patient requiring respirator treatment in detail elsewhere and shall make only a few

additional comments. It has been suggested that patients be placed in the respirator several hours each day during their convalescence, that is, after their respiratory function has returned sufficiently to enable them to breathe spontaneously. We were able to do this with one patient, and the result was most encouraging. In the acute stage some of our patients were given convalescent serum and others received ephedrine intratheeally. The small number so treated prevented a suitable evaluation of either form of therapy. Deaths occurred among patients who received serum in the preparalytic stage. Ephedrine sulphate administered in the paralytic stage seemed to benefit some patients, whereas in others it apparently had no effect.

# RESULTS

Bulbar Cases.—All of the twelve patients with bulbar lesions and injury of the respiratory center died. Four of them died within twenty-four hours, and five others within three hours after being placed in the respirator.

TABLE II

SIXTY-THREE CASES TREATED IN RESPIRATORS. THE MORTALITY DURING TREATMENT AND THE TOTAL MORTALITY ACCORDING TO THE TYPE OF LESION AND THE YEAR OF TREATMENT

YEAR	TYPE OF NUMBER TREATED		DIED DUE PIRATOE MI		DIED AFTER DIS-	TOTAL DEATHS		
			NUMBER	PER CENT	CHARGE	NUMBER	PER CENT	
1931	Spinal Bulbar	34 12	16 12	41 100	10	26 12	76 100	
1932-33	Spinal	17	8	41	2	10	59*	
Total		63	36		12	48		

<sup>\*</sup>Exclusion of the patient who died of neutropenia brings the total percentage of deaths to 53.

Spinal Cases.—Twenty-four of the fifty-one patients with spinal lesions died in the respirator, ten in less than twenty-four hours, and two in less than three hours. Obviously many of the patients arrived at the hospital too late for any possible benefit from artificial respiration, and this accounts in part for the high mortality which we had. Twenty-seven patients left the hospital alive.

The immediate mortality\* among patients with respiratory embarrassment from spinal lesions due to poliomyelitis who have been treated in the Drinker respirator has been the same in each of the epidemic years under consideration (Table II). However, the ultimate mortality during comparable follow-up periods has decreased. Thus, during a period of two years after surviving their respirator treatment there were eight deaths among eighteen patients in the 1931 group (two more died after

<sup>\*</sup>Immediate mortality includes those deaths which occurred during respirator treatment; ultimate mortality includes those deaths which occurred after respirator treatment and were possibly related to the respiratory paralysis or the treatment.

PATIENTS WHO SURVIVED. COMPARISON OF CONDITION OF PATIENTS WHEN RESPIRATOR TREATMENT WAS BEGUN WITH CONDITION AFTER TWO TO FOUR YEARS

CASE NO., HOSPITAL NO., AND AGE AT ON- SET OF HELNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CON- DITION WHEN REEXAMINED*
1 4912 S yr.	Admitted on the third day of illness, acutely ill. Temperature 103.6° F.; nasal voice, difficulty in swallowing; neck and back stiff; paresis of neck muscles; hyperactive deep reflexes. On third day in hospital movements of diaphragm weak, slight respiratory difficulty. Following day restless, perspiring, cyanotic; paralysis of diaphragm. Placed in respirator for 18 hr., after which she was able to breathe spontaneously with only her intercostal muscles.	After 2 yr.: Active, normal child. No evidence of paralysis. Breathes normally; good cough. The child had made a complete recovery at the end of one year.
2 5000 8 yr.	Admitted on second day of illness with preparalytic poliomyelitis. Convalescent serum given intravenously. Third day in hospital paralysis of upper extremities; fourth day paresis of lower extremities; breathing almost entirely abdominal, voice weak. In respirator for 10 days.	After 3 yr. and 10 mo.: As active as any other child—runs, jumps, skates, rides a bicycle, and plays ball. Some atrophy and slight weakness of left deltoid but no limitation of motion. Left hand grip a little weaker than right. Slight weakness of abdominal muscles. Breathing both thoracic and abdominal. Has had no intercurrent illnesses.
3 20 S yr.	Admitted on ninth day of illness. Had been in another hospital for 5 days where he become progressively worse. On admission he was cyanotic, gasping for air; had received artificial respiration in ambulance. Placed in respirator immediately after admission. Following day examination revealed weakness of neck and back muscles; quadriplegia; paralysis of upper intercostals. In respirator 3 days.	After 3 yr. and 8 mo.: Attended orthopedic clinic for a year, and last report stated that patient was discharged as completely re covered.
4 4791 9 yr.	Admitted on the fourth day of illness after a trip of 80 miles. Acutely ill; temperature 103° F; nasal voice; difficulty in swallowing; slight left facial weakness; left side of palate weak. Unable to sit up; generalized flaceidity with rigid neck and back. No cyanosis or dyspaea. Following day there was more prostration and some restlessness. Beginning weak-	After 2 yr. and 3 mo.: Well-de veloped and active child; up and about. Slight weakness of left lower facial muscles and asymmetry of soft palate. Breathes, talks, and swallows normally except for slight huskiness of voice. All other muscles normal. Has had several attacks of bronchitis, some of which were prolonged.

<sup>\*</sup>Nineteen patients were reexamined by one of us, the last examination after the time interval indicated. Patients 3 and 15 were not examined by us, but we obtained a report of their last examinations through the courtesy of the orthopedic hospital which they attended.

# TABLE III-CONT'D

	TABLE TIE	
CASE NO., HOSPITAL NO., AND AGE AT ONSET OF HUNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CON- DITION WHEN REEXAMINED*
4 4791 9 yr. Cont'd	ness of diaphragm and inter- costal muscles. Slight cyanosis relieved by oxygen. Next day diaphragm paralyzed, and cy- anosis persisted, therefore pa- tient was placed in respirator. Had stormy course due to in- ability to swallow saliva and mucus. In respirator for 2 pe- riods of 5 and 4 days, each with an intervening interval of 20 hr.	
5 5214 3 yr.	Delirious, dyspneic, no thoracic movement; suprasternal retractions, weak muscles of neck and back; paresis both lower extremities and of left upper. Placed in respirator 4 hr. after admission on the fourth day of illness. In respirator 14 days.	After 4 yr. and 3 mo.: Well-developed, alert child as active as any her agc. Attends school. Examination shows weakness of left intercostals and muscles of left shoulder and arm with some atrophy. Slight scoliosis is present.
6 4830 12 yr.	Quadriplegia; weakness of neck and back muscles. Breathing with great difficulty using only diaphragm. Feeble voice, drowsy, perspiration, slight cy- anosis. Used accessory muscles of respiration. Was in respira- tor 3 weeks. During respirator treatment developed massive at- clectasis of right upper lobe.	Attends high school—walks two miles to and from school each day. Uses upper extremities for all necessary movements, in spite of advanced atrophy of muscles of both arms. Has a marked scoliosis and atrophy of
7 5349 14 yr.	Quadriplegia, rigid neck. Shallow breathing, no thoracic and little abdominal movement; used accessory respiratory muscles; talked in a whisper; slight cyanosis. Placed in respirator or admission—the seventh day of his illness. In respirator 4 days.	well except for slight lag of left leg. Almost complete flaceid pa- ralysis of right upper extremity. Atrophy of muscles of the right upper chest and shoulder. Sco- liosis—patient wears brace. No
8 539 <u>2</u> 10 yr.	Quadriplegia. Temperature 105; F.; feelde pulse; drowsy; facedusky; petcehial rash; diletation of alae nasi; barely audible toice; no movement of thorax Convalescent serum had been administered on two successive days preceding admission. It respirator 3 weeks.	cheerful hoy, rble to sit up in wheel chair. Can walk a little with aid of crutches. Writes; feeds and clothes himself. Tutor comes to home. Weeks a

# TABLE III-CONT'D

CASE NO., HOSPITAL NO., AND AGE AT ON- SET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CON- DITION WHEN REEXAMINED
9 5056 12 yr.	Admitted on the second day of illness with paralysis of both lower extremities and paresis of both upper extremities. Neck and back stiff; abdominal reflexes absent. Acutely ill but without respiratory embarrassment. Following day quadriplegia and extensive intercostal paralysis; voice weak; color poor. Placed in respirator. Had a stormy course with prolonged periods of cyanosis in spite of oxygen. Later developed paralysis of diaphragm. For the first 20 days respirator could be stopped for only few minutes at a time. In respirator 7 wk.	After 2 yr.: Shoulder muscles weak but moves forearms and hands well. Feeds herself and is able to write and turn pages of books. Poor function and atrophy of muscles of lower extremities. Gets a bout in wheel chair. Some spinal curvature. Respirations mostly abdominal but she breathes easily, cough fair, voice normal. School subjects taught by visiting teacher. No intercurrent illnesses.
10 6459 5 yr.	Rapid shallow breathing due to weakness of thoracic muscles and diaphragm; voice good. Weak neck and back muscles. Paralysis of lower extremities and paresis of upper extremities; distended bladder. Twenty-two hours after admission (sixth day of illness) placed in respirator because of practically no movement of thorax, dilatation of alae nasi, perspiring, and color poor. In respirator 19 days.	After 3 yr. and 10 mo.: Shoulders weak; forearms and hands have good function. Feeds herself and turns pages of books. Paralysis of lower extremities—she wears a brace. Can sit up and stand a little. No difficulty in breathing; speaks clearly; cough is fairly loud; respirations are thoracic and abdominal; respiratory capacity is diminished. No intercurrent illness.
11 4304 8 yr.	Admitted on sixth day of illness with weak neck and back muscles. Paresis of lower extremities; absent abdominal reflexes. Two days later spread of paralysis involving intercostals. Following day he was apprelensive, voice weak, slight dyspnea, diminished intercostal movement; color good. Placed in respirator for 20 hr.	After 3 yr. and 10 mo.: Flaceid paralysis of lower extremities, shoulders weak, spinal curvature. Can sit up, feed himself, and turn pages of books. Chest well developed. Thoracic excursion during respiration is symmetrical but diminished. Cough is fairly loud. Several colds but not of long duration. Appendectomy under inhalation anesthesia 4 mo. ago. Uneventful recovery. During his early convalescence this patient had massive atelectasis.
12 4893 11 yr.	Admitted on sixth day of illness. Acutely ill, wenkness of lower extremities, back and neck; abdominal and all deep reflexes absent. Following day weakness of both shoulders and intercostal museles. Two days later quadriplegia, distended bladder. Shallow abdominal respirations, spoke only in a whisper; slight	a wheel chair. Cannot walk but is able to stand with braces. Paralysis and atrophy of shoulder muscles. Fair function of forearms and hands; feeds himself and reads books. Poor function of lower extremities. Spine straight. Respirations

TABLE III-CONT'D

CASE NO., HOSPITAL NO., AND AGE AT ONSET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CON- DITION WHEN REEXAMINED		
12 4983 11 yr. Cont'd	cyanosis. In respirator 3 wk. Three months after discharge had massive atelectasis with convulsions, cyanosis, and stupor. Mental impairment persisted for several months.	easily. No illness during past year.		
13 6158 7 yr.	Transferred from another hospital on tenth day of illness. Acutely ill, gasping for air, cyanotic, temperature 102.2° F. Quadriplegia, weak neck and back muscles. Paralysis of lower intercostals and diaphragm. Placed in respirator immediately and oxygen administered. This patient received prolonged respirator treatment (6 mo.) after he could breathe without artificial respirator. Was dependent on the respirator for 8 wk.	After 2 yr.: Fair function in right forearm and hand. Impaired function left lower and left upper extremities. Neck muscles strong. Able to remain in sitting position when so placed. Slight scoliosis present. Breathes normally and has a good cough. Slight atrophy of muscles of right upper chest and shoulder. No illness during past year. A bed patient.		
14 4894 11 yr.	Admitted on fourth day of illness with weakness of upper extremities which progressed to paralysis on the next day. The following day there was weakness of the lower extremities and paralysis of the diaphragm. He was using the accessory muscles of respiration and was slightly cyanotic. Respirator treatment for 4 wk.	good; is comfortable and happy. Normal respiratory function. Limited movement of left upper extremity. Paresis of right upper and both lower extremities except feet and forearm. Sits up unaided. Able to swim in pool. Patient stated		
15 4556 10 yr.	Quadriplegia. Restless; shallow rapid breathing due to weakness of intercostals and diaphragm Placed in respirator immediate ly after admission on the sixtl day of illness. In respirator 1 days.	of all extremities with only traces of muscle power. Unabla to support trunk; spinal curvature. A bed patient.		

two and one-half years) compared to two deaths among nine patients in the 1932-1933 group. This decrease in the ultimate mortality, we believe, is due partly to greater familiarity in handling the respirators. An important factor is that since the epidemic of 1931 the incidence of poliomyelitis in New York City has diminished and the number of patients requiring respirator treatment has decreased permitting better care of the individual patient.

# VALUE OF THE RESPIRATOR

The value of respirator treatment has been questioned by some because of the high mortality and because many of the survivors are seriously crippled. In a recent article<sup>10</sup> it was shown statistically that the mor-

tality in a group of patients treated in the respirator was higher than in a group of supposedly comparable patients not so treated. The material for this statistical comparison was obtained from the charts of cases in four of the contagious disease hospitals in New York City. The necessary data were transcribed from the hospital charts onto a prepared form. From these forms cases with respiratory embarrassment not treated in the Drinker respirator were selected as a control group for comparison with a group treated in the respirator. The inherent error which occurs when a large number of persons, some unfamiliar with the patients, abstract and transcribe data from hospital charts is obvious. In evaluating a form of therapy, especially in a disease as variable as poliomyclitis, it is essential to observe personally all the patients—treated patients as well as untreated controls.

During the last four years we have observed numerous patients with respiratory embarrassment who were not treated in the respirator. After careful study it was evident that in our untreated cases as a group the paralysis was not as extensive, nor the illness in general as severe, as in the cases treated in the respirator. Consequently, they could not be used as a control group for comparative analysis.

Some of our patients, who would have died without respirator treatment, have practically no residual paralysis today (Table III). Others are partially incapacitated but are able to attend school. Unfortunately, others are greatly handicapped in the use of their extremities. Since no one can foretell which patient with respiratory failure will regain the use of his extremities or trunk muscles, all properly selected patients should receive the benefit of treatment in the respirator.

# COMMENT AND SUMMARY

Analysis of the results obtained in sixty-three cases treated in the Drinker respirator indicates that the proper selection of patients for treatment is necessary. This is of especial importance in epidemic periods, when the number of respirators available is usually less than the demand. We have found the respirator useful only in patients with paralysis of the respiratory muscles due to lesions in the spinal cord. The patients with injury of the respiratory center who were treated in the respirator all died. Such patients, as well as those with obstruction of the upper air passages due to the inability to swallow saliva, mucus, or vomitus, do better when treated by other methods.

Patients with spinal cord lesions which cause paralysis of the diaphragm or thoracic muscles and who have definite signs of respiratory difficulty should receive treatment in a respirator. On the other hand, patients with slight evidence of respiratory embarrassment without dyspnea or cyanosis should not be placed in a respirator. Our opinion is based on the present knowledge of the physiology of respiration, the pathologic pulmonary conditions found in patients after treatment in

the respirator, and the late pulmonary complications occurring in patients who survived the respirator treatment. However, when a patient has any involvement of the respiratory muscles or evidence of an ascending paralysis, he should be in a hospital near a respirator because there is no way of telling whether the condition will become worse.

Follow-up data were obtained in all twenty-seven patients who were discharged from the hospital. Some recovered use of their paralyzed muscles and are normally active children; others are handicapped but are able to get about; and several are bedridden. After leaving the hospital, eleven patients died from some pulmonary condition, but in only two of these were roentgenograms taken. These were the only two fatal cases in which a diagnosis of massive atelectasis was made. ically atelectasis is frequently mistaken for pneumonia, and in some of the nine patients in whom a diagnosis of pneumonia or pulmonary edema was made, the history strongly suggested the possibility of atelectasis. Massive atelectasis developed but was not fatal in five patients. we have the occurrence of massive atelectasis in seven (and possibly in others) of the twenty-seven patients who survived their original respiratory paralysis.

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# BACILLUS ACIDI LACTICI MENINGITIS IN A NEWBORN INFANT

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THIS case is reported because of its rarity. There are only four other reports of meningitis due to Bacillus acidi lactici in medical literature, two being in newborn infants, one in a premature infant one month old, and one in an adult. There are only five references to infections from this bacillus in any part of the body.

## REPORT OF CASE

In order to discuss more thoroughly the possible portal of entry of infection in this case, it is essential to report the antepartum course of the mother.

M. P., married, aged twenty-seven years, para i, gravida iii, gave the significant past history: (1) acute cervical adenitis as a child; according to the patient, cultures from these glands revealed a colon bacillas; (2) one spontaneous abortion in 1932 in the second month; (3) one full-term baby born in 1933 in Italy. The delivery was spontaneous after a nontoxic course, and the birth weight was five pounds. This child died at the age of eighteen months with a diagnosis of encephalitis lethargica.

Antepartum Course.-The patient was first seen by one of us (L. L. M.) on Nov. 12, 1934. At this time the physical examination was negative excepting for a smoothly enlarged thyroid and sinus arrhythmia. The course of her pregnancy was uneventful until Feb. 18, 1935. She then developed an acute vaginitis with excoriation of the mucosa. Fresh preparations were negative for Trichomonas vaginalis and smears were negative for gonococci. Potassium permanganate douches (1:4,000) were prescribed and local treatment applied. The discharge was repeatedly studied and gram-negative bacilli were found in almost pure culture. As the leucorrhea persisted and as the case clinically simulated trichomoniasis, an insufflation of stovarsol was given on March 18, 1935. Approximately three minutes after the insufflation the patient fainted. She was placed on a table in Trendelenburg position, and her breathing became loud and stertorous. Rigidity ensued, and she went into a severe tonic spasm with marked carpopedal spasm. Cyanosis was intense; the pulse was imperceptible; breathing ceased; and she gradually receded into a state of asphyxia pallida and appeared lifeless. One cubic centimeter of adrenalin was injected intramuscularly, and artificial respiration was begun. In about three minutes she took a deep breath, and spontaneous respiration was soon reestablished. For an hour she appeared dazed but gradually recovered consciousness and was able to leave the office two hours after the seizure. The blood pressure was 102/64 prior to the insuffation and rose to 120/80 two hours later.

The next day (March 19, 1935) she began to have labor pains although her date of confinement was calculated as May 2, 1935. She was immediately taken to York Hospital where, after a labor of eight hours, she was delivered spontaneously of a five-pound girl. The infant cried immediately and appeared healthy for its size.

Read before the New York Academy of Medicine Section of Pediatrics, May 9, 1935.

The postpartum course was uneventful, and the patient left the hospital after an afebrile puerperium. The antepartum vaginitis did not recur. On May 10, 1935, a small erosion about the external os was noted, and four days later under sterile precautions this erosion, the cervical canal, and the vaginal walls were cultured. Endo's agar plates were sterile, but blood agar plates showed almost pure cultures of Streptococcus hemolyticus, an occasional Staphylococcus albus hemolyticus, and a few colonies of Bacillus coli communis.

Clinical Course.—One of us (J. D. C.) first examined the baby six hours after delivery and found her to be negative physically. She was placed on a formula consisting of powdered milk modified with lactose—one ounce of the mixture being given every two hours. The feedings were taken well by a Breck feeder. After four days the formula was concentrated and the feeding intervals lengthened. Her course was uneventful until the eighth day, and there was no vomiting at any time.

On the eighth day the child began having periods of sudden marked generalized cyanosis lasting from 15 to 90 seconds. Respirations during these attacks were reduced to an average of three to five per minute. The institution of oxygen and 5 per cent carbon dioxide immediately cleared the existing cyanosis. Physical examination during and between attacks was negative except for the cyanosis and the reduction in respiratory rate. The fontanel was at no time full; there were no pathologic neurologic findings and at no time was there an elevation of temperature. With the onset of these attacks the infant refused food and gavage was started. Still there was no vomiting. In the next sixteen hours there were eight similar seizures. The infant was moved to the Babies Hospital where she was placed in an oxygen tent and fed breast milk from a Breck feeder.

On the tenth day after twelve hours in the Babies Hospital, the last hour of which she had been out of the oxygen tent, the baby had had no cyanotic attacks, and the temperature and physical examination remained normal. Breathing was not appeared, and she took the feedings well. Throughout the eleventh day her condition remained the same.

Upon the morning of the tweifth day the baby had five attacks in four hours consisting of generalized blushing, screeching, and waving both arms and legs, the left more than the right.

Following these attacks she held her breath and became cyanotic. The fontanel for the first time was slightly full, and the heart and respirations were irregular. Lumbar puncture revealed thick yellow tenacious pus containing four-plus globulin and a gram-negative organism.

On the thirteenth day the child had many convulsions and was fed by a medicine dropper. A second spinal tap yielded pus again. The laboratory reported Bacillus acidi lactici from the spinal fluid obtained the day before.

On the fourteenth day the child was moribund and died late in the day. No intraspinal therapy was attempted.

An autopsy was performed fourteen and one half hours postmortem. The anatomical diagnoses were as follows: acute pachymeningitis; acute ependymitis; acute purulent of this media—right—Streptococcus hemolyticus; lobular pneumonia—right; accidental involution of thymus; angiomatoid nodules on tricuspid and mitral valves, patent foramen ovale; anomalous fissuration of lungs; azygos lobe; dilated carum septi pellucidi and septi Vergal.

Final Autopsy Note.—A case of Bacillus acidi lactici meningitis in which the portal of entry could not be determined. Acute office media was considered at autopsy as a possible focus, but cultures and Gram stains of sections from the right middle car demonstrated a streptococcus. The pneumonia, undoubtedly a terminal feature, was due to a gram positive coccus morphologically a streptococcus.

# COMMENT

Bacillus acidi lactici is a gram-negative bacillus belonging to the colon bacillus group. It is found in the intestinal canal and is considered to be a harmless saprophyte without pathogenic significance. It may be present in water and may be present in milk.

Greenthal<sup>2</sup> reported a case of *Bacillus acidi lactici* meningitis occurring in a premature negro girl aged one month. Death occurred on the eighth day after the onset of symptoms, and at postmortem *Bacillus acidi lactici* was recovered from the exudate on the surface of the brain and from a purulent discharge from the right middle ear.

At a meeting of the American Pediatric Society Sherman<sup>3</sup> reported a fatal case of purulent meningitis in a newborn infant due to a gramnegative bacillus. The bacillus was not identified with any known pathogen. The description of the organism and its cultural characteristics undoubtedly classify it as *Bacillus acidi lactici*, and Neal<sup>4</sup> regarded it as such.

Ray<sup>5</sup> described a case in an adult, aged fifty-five years, with a positive blood culture of *Bacillus acidi lactici* and a positive culture of the spinal fluid on two occasions. At postmortem examination the organism was recovered from the viscera and from the brain.

Pasachoff's reported a case in a newborn infant in whom the symptoms started on the tenth day of life and death occurred thirteen days later.

Morphologically Bacillus lactis acrogenes is the most similar of all bacilli to Bacillus acidi lactici; however, the former can be readily differentiated by its ability to ferment saccharose. Meningitis due to Bacillus lactis aerogenes has been found in three instances.

In analyzing more than 1,500 cases of meningitis seen by the Meningitis Division of the Research Laboratory of the Department of Health of New York City up to 1924 Neal\* found only five cases due to the colon bacillus group, none of these due to the Bacillus acidi lactici. In 1934 in a group of 623 cases of meningitis other than those due to the meningococcus or Bacillus tuberculosis, she<sup>s</sup> found none due to Bacillus acidi lactici. The only other reference to infection from this bacillus in the literature is a report of two adult cases of acute bacterial endocarditis reported by Dickar. Neither of these patients recovered.

Mode of Entry of Infection.—In view of the fact that the autopsy findings did not reveal the portal of entry, the following are necessarily merely interesting theories.

1. That the focus was a prenatal infection of the mother. Dandy and Blackfan<sup>10</sup> expressed belief that intrauterine meningitis is not infrequent and in many cases is an etiologic factor in the production of hydrocephalus. The fact that in our case the infant did well for the first eight days tends to rule out this possibility; however, one must

not forget the tonic spasm of the mother immediately preceding labor in regard to a low grade discharge in which, among others, gramnegative bacilli were found in almost pure culture.

- 2. Infection from the otitis media. The culture of streptococcus from the ear at autopsy eliminates this.
- 3. Infection through the lymphatics or by direct extension from contiguous foci in the nose or mouth may be possible; however Bacillus acidi lactici is not ordinarily an inhabitant of these areas at this early age.
- 4. Premature respirations with aspiration of contaminated liquor amnii through the eustachian tube might be considered as a portal of entry had the symptoms begun earlier.
- 5. Milk-borne infection might have been possible, but the food was not cultured.

The explanation may lie in the aforementioned theories, but we have not enough evidence to draw any definite conclusions.

Treatment.-In none of the cases reported nor in our case was intraspinal therapy attempted. If a case were diagnosed early enough and if the patient were in condition to stand the shock of intraspinal therapy a polyvalent Bacillus coli bacteriophage could be logically used..

# SUMMARY

A case of meningitis due to Bacillus acidi lactici in a newborn infant is reported. Review of the literature shows that only four instances of meningitis due to this organism have been reported. Three were in newborn infants and one in an adult, and none survived. The possible portals of entry are considered.

We desire to thank Dr. Herbert Wilcox for his help and for allowing us to report this case. We also thank Dr. Martha Wollstein for her excellent autopsy report.

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- - 33 EAST GIST STREET
  - 535 PARK AVENUE

# INTERPRETATION OF ROUTINE BLOOD CULTURES IN YOUNG INFANTS

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IN A PREVIOUS report from this clinic, Dunham has shown that A bacteremia in the first month of life is not a rare occurrence.3 In the cases she studied, the mortality was high, and in many instances the mode of entry of the infection was not obvious, and the classic signs of sepsis were absent. As a result of these observations, the present investigation was undertaken in which blood cultures have been taken routinely in obscure illnesses of young infants as well as in cases of obvious infection. Postmortem cultures have been done regularly within twenty minutes of death. The findings in this study may help to answer certain questions concerning the practicability and value of routine blood cultures in this age period and the significance of positive cultures. The chief questions which arise have to do with the difficulty of taking blood and the frequency of contamination, the possibility of clinical recognition of cases of generalized infection, the prognostic significance of a positive blood culture, and the actual part played by infection in a given case.

In interpreting the results of these blood cultures, the term bacteremia has been applied only to cases in which a pathogenic organism was demonstrated either on two successive cultures or on broth and plate from one sample of blood. Postmortem blood cultures have been interpreted conservatively, not because of postmortem dissemination of organisms, which would be negligible within twenty minutes after death, but because on its way to the heart the needle may pick up organisms from the lung. Accordingly, the postmortem culture has been accepted as the sole proof of bacteremia only when there are over 200 colonies in the 1 c.c. pour plate. Staphylococcus albus and Streptococcus viridans have been regarded as contaminants unless present in both broth and pour plate. There is no difficulty in recognizing the other common contaminants.

In the period from June 1, 1932, to Jan. 30, 1934, blood cultures were done on 114 infants not more than one month old. In 96 cases the blood cultures yielded nothing of significance. In 20 of these cases the only cultures were taken postmortem, and of these, 15 showed no growth, 4 showed staphylococcus, and 1 Streptococcus viridans. In the remaining 76 cases, 116 cultures were taken, all during life; 105 of these were sterile, staphylococci were found in 15, diphtheroids in 3, Streptococcus viridans in 2, and B. sublitis in 1. These figures illustrate the practicability of routine blood cultures in young infants and show

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that an agonal bacteremia is not invariable. There were only 2 deaths in the group of 76 cases just mentioned.

In 18 cases pathogenic organisms were found; death occurred in 16 of these, and in all 12 of those in which the criteria given above were fulfilled In 3 of these 12, the only cultures were taken postmortem, but the other 9 cases illustrate the ominous prognostic significance of a positive blood culture. Evidently generalized infection was not the explanation of the symptoms which led to the taking of a blood culture on the 76 "negative" cases.

Brief histories of the 12 cases fulfilling all our criteria for "bacteremia" are given, and the principal clinical, pathologic, and bacteriologic findings are summarized in Table I. Streptococcus hemolyticus was the predominant organism in 5 cases, and B. coli in 2 cases.

TABLE I
IMPORTANT CLINICAL, ANATOMIC, AND BACTERIOLOGIC FINDINGS

PA- HENT	LESIONS NOT DUE TO INFECTION	LESIONS DUE TO INFECTION*	BLOOD CULTURES
1		Erysipelas Serotal ab scess (Streptococcus hemolyticus)	Streptococcus hemolyticus
2		Enysipelas, cellulitis, pel- vic abscess, peritoritis (Streptococcus hemolyticus)	Streptococcus hemolyticus postmortem culture showed Streptococcus hemolyticus + B. coli
3		Erysipelas, peritonitis (Streptococcus hemolyticus)	Streptococcus hemolyticus
1	Hemangioma of mitral valve	Nonsuppurative encepha lopathy,† pneumonia	Streptococcus hemolyticus
5	Mongolian idiot, imperforate an us, erythro blastosis fetalis	Cellulitis of abdomen and legs	Streptococcus hemolyticus
6	Mongolian idiot, hydroureter	Pyelonephritis (B coli), endocarditis	B coli
7	Extradural hemat	Meningitis (B co't)	B. coli
4	Prematurity, atelectasis, in traventricular hemorrhage	Laryngitis, bronchitis, fo- cal pneumonia, nodules in liver and spleen	Organism unidentified
Đ		Meningoanguitis (organism unidentified), hemor- rhagic encephalomical itis, focal necrosis of his er and spleen	Surie organism as in Case S
10		Meningitis (pneumococcus Type V), otitis media	Pneumococcus Type V
11	Melectures		Streptococcus viridans
1.2	!	Purpura, meninococcemia	Meningococcus

In most instances these lesions were probable due to the organism found in the blood stream. Cultures made from the actual lesions are given in this column in parentheses. Thus 'Scrotal abscess Str. hemoluticus' indicates that streptococci were cultures from the abscess itself.

<sup>\*</sup>It is not certain whether this lesion should be attributed to infection or to cerebral

An interesting organism, not previously identified, was recovered in 2 It is a hemolytic gram-positive rod, apparently closely related to an organism isolated from hemorrhagic encephalitis of calves 2,4 Streptococcus viridans, pneumococcus type V, and meningococcus were obtained in one case each. In a number of instances the result of the blood culture was a surprise Apparently routine blood cultures must be taken of sick infants if cases of generalized infection are not to be missed In few of the cases given here was the pathway of infection obvious The one item which stood out as a predisposing factor was the presence of grave congenital or other preexisting lesions. However, in 6 of the cases all the major pathologic changes seemed attributable to infection. In one instance in which green streptococci were recovered in large numbers, the organisms probably had little to do with the infant's death In all other cases significant bacterial lesions were demonstrated.

# CASE REPORTS

CASE 1—I. B, circumcised twentieth day; twenty third day, red area on thigh. Admission on twenty sixth day with extensive erysipelas and several abscesses in scrotum. Death on twenty eighth day, no autopsy. Culture of scrotal abscess, hemolytic streptococcus. Postmortem blood culture, 2,000 colonies hemolytic streptococcus in 1 c.c. pour plate

CASE 2—A. L, showed swelling of scrotum on twenty sixth day. Admitted thirtieth day with extensive erysipelas Blood culture, hemolytic streptococcus Death on thirty first day. Postmortem cultures from heart, umbilicus, scrotum, and peritoneum showed a mixture of hemolytic streptococcus and B. coli. Anatomic diagnosis: Cellulitis of periumbilical tissues and scrotum, desquamative dermatitis of trunk and legs, pelvic abscesses, scrofibrinous peritonitis, and hemorrhage into intestinal wall and both adrenals. Subsidiary: Patent foramen ovale, multiple lymphangicctases of intestines, and fibrosis of pancreas.

Case 3—F. M, well until thirteenth day when abscess was noted in vulva. Admitted nineteenth day with widespread erysipelas. Grew rapidly worse, developed signs of peritonitis, died on twenty second day. Postmortem cultures of blood and peritoneal fluid showed hemolytic streptococci.

CASE 1.—B, pule and drowsy at birth, with irregular respiration. Third day, fever, right facial palsy, spasticity of left arm. No fluid obtained on lumbar punc ture. Antemortem and postmortem blood cultures showed hemolytic streptococcus. Death on fourth day. Anatomic diagnosis: Extensive necrobiosis, demyelinization, and glial proliferation in brain; confluent focal pneumonia (bilateral), pulmonary congestion, and hemorrhage. Subsidiary: Hemangioma of mitral valve.

Case 5—C, mongolian idiot, admitted to hospital on first day because of absence of anus, was deeply jaundiced. After repair operation, there was rapid development of cellulitis of legs and abdominal wall, although the site of operation looked normal. Many normoblasts in peripheral blood. Antemortem and postmortem blood cultures showed hemolytic streptococci. Death on third day. Autopsy. Anatomic diagnosis: (a) Cellulitis of abdomen and legs, congestion and hemorrhage in lungs, liver, testes, adrenals; jaundice (b) Congenital anomaly of rectum; recent operation (repair of imperforate anus). Subsidiary: Patent ductus arteriosus

Case 6—D. H, a mongolian idiot, developed diarrhea and dermatitis at seven days. On the tenth day a specimen of urine showed pus; on the seventeenth day a blood culture showed B coli. The diarrhea continued; fever developed in the fifth week, and death occurred on the thirty minth day. Autopsy. Anatomic diagnosis

Pyelonephritis (bilateral), hydroureter (bilateral); acute mitral endocarditis. Subsidiary: Mongolian idiocy.

CASE 7 .- D., a full-term infant, delivered by version and extraction, seemed well until the fourth day, when she became feverish. On the sixth day the temperature was 39° C., and the fontanel was bulging; the child died rather suddenly. Postmortem cerebrospinal fluid showed B. coli on smear; blood and cerebrospinal fluid cultures, B. coli. Autopsy. Anatomic diagnosis: Purulent meningitis, pulmonary Subsidiary: Patent ductus atelectasis, extradural hematoma (right temporal). arteriosus, foramen ovale, and bicornate uterus.

CASE 8,-C. A. M., born with cord around neck, admitted first day with cyanosis, irregular respiration, nasal discharge, coarse râles, impaired percussion note on left. Weight 2,175 gm. Death one-half hour after admission. Postmortem blod culture showed a hemolytic gram-positive bacillus, as described in the report by Burn. Autopsy. Anatomic diagnosis: Acute laryngitis and bronchitis, focal pneumonia (bilateral), pulmonary atelectasis and emphysema (bilateral), petechiae in pleura, focal proliferative nodules in liver and spleen.

CASE 9 .- M. D., developed diarrhea on sixth day; ninth day feverish, refused feeding, admitted to hospital. Weight 3,120 gm.; temperature 101.8° F. Child was drowsy and spleen palpable. On the tenth day blood culture showed an organism identical with that found in Case 8. The child became increasingly drowsy, and meningeal signs appeared. No fluid obtained in lumbar puncture. Autopsy. The organism found on blood culture was demonstrated in the meninges both by culture and smear. Anatomic diagnosis: Suppurative meningoangiitis, suppurative hemorrhagic encephalitis and myelitis, cerebellar pressure cone, focal necrosis, and hemorrhage in liver and spleen.

CASE 10 .- D. V., full-term infant, developed "heavy breathing" on the eighth On the tenth day he had a convulsion and was brought to the hospital. Temperature 39.6° F.; respirations labored, fontanel bulging; both ears full. Cerebrospinal fluid showed innumerable pneumococci (type V). Death on twelfth day. No autopsy.

CASE 11 .-- M. M., mother had a convulsion after forty-eight hours of labor; the cervix was dilated manually and the infant delivered by high forceps. The child was cyanotic, with irregular respirations, much mucus, bilateral atelectasis, and facial palsy. Death on first day. No autopsy. Postmortem blood and spinal fluid cultures revealed Streptococcus viridans in large numbers.

Case 12 .- M. N., had a "cold" on the twentieth day. On the twenty-sixth day he developed fever and diarrhea. The next day there was an extensive pupuric eruption, and child was brought to hospital. Blood smears showed intracellular diplococci. Meningococci were cultured from the blood, nose and throat. Cerebrospinal fluid 45 cells, all lymphocytes, Pandy 2+, culture, no growth. The child died shortly after admission.

# CONCLUSIONS

- 1. The experience recorded here indicates that blood culture is a practical and useful diagnostic procedure during the first month of life.
- 2. The course of some of the cases cited is rather bizarre. Nevertheless, a positive blood culture in a young infant indicates a bad prognosis, and in most instances the rôle of the organism is not merely passive.

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# EDEMA IN INFANCY AND CHILDHOOD AS AN EXPRESSION OF CHRONIC DIETARY INSUFFICIENCY

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THE epidemic occurrence of generalized edema in people suffering from famine following the World War served to focus attention on dietary deficiency as a cause of the condition. This type of edema has been produced experimentally in animals and has been extensively studied in both experimental and clinical subjects. It has been found to be characterized by hypoproteinemia and to result when the diet for a long time is deficient in protein and caloric value and high in water and salt content.

At present except in districts where famine is endemic, it is unusual to see more than occasional isolated instances of the sort of generalized edema originally described. The edema occurs in cachectic individuals or is seen in association with some chronic disease of the gastrointestinal tract. During the nine years that the authors have worked in Tennessee they have been impressed by the occurence of edema in children who were not extremely malnourished and who were not critically ill. children were of families in a poor economic status and were those who presented themselves to our clinic for treatment. Occasionally there was no disease found other than malnutrition. More frequently the edema was found in patients with diarrhea or dysentery or some parenteral infection. At first these cases were observed and treated without making chemical studies of the blood. An occasional determination of total serum protein was made and the level found considerably reduced. Youmans' study showed that nutritional edema was endemic in the medical out-patient group of this hospital. It seemed probable that the local dietary habits, poor economic status, and the prevalence of diarrhea were combining to make edema of nutritional origin a fairly common occurrence among the children as well as the adults. We studied therefore, the serum proteins on all cases of edema which we saw. The results of the studies on patients in whom there was neither cardiac nor renal disease are presented in this paper.

# LITERATURE

No attempt will be made to review all of the scattered and voluminous literature on nutritional edema. Maver<sup>2</sup> gave an interesting description of the condition which was prevalent in parts of Europe following the

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World War. Ling<sup>3</sup> and Weech and Ling<sup>4</sup> investigated more fully a similar condition in patients from famine districts of China. By the time their investigation was made, deficiency of protein in the diet and decreased protein content of the blood serum were recognized as important factors in the production of edema.<sup>5, 6</sup> In the study of eighteen patients with generalized edema Weech and Ling<sup>4</sup> found that the serum proteins were invariably much reduced. Later work<sup>7, 6</sup> emphasized the greater importance of albumin as compared to globulin in maintaining a normal colloidal osmotic pressure in blood serum to regulate the fluid equilibrium between blood and tissues. When serum proteins are reduced as a result of dietary insufficiency, the loss is mainly in the more important albumin fraction.<sup>9</sup>

Most of the work on serum proteins reported in the literature has been done on the serum of adults or of experimental animals. It has been shown, however, that infants have a lower level of serum protein with a higher percentage of the total in the form of albumin than is true of older children.<sup>10</sup> It is generally agreed that at about two years of age, or when the diet becomes a general one, the serum proteins of children reach approximately the levels found in normal adults.<sup>11-12</sup>

Pediatric literature contains many scattered statements and figures indicating that acute and chronic infections in general, as well as various types of diarrhea, tend to lower the serum proteins, mostly at the expense of the albumin fraction. Webb¹⁴ concluded that malnutrition in itself had no effect on the level of serum proteins in children although he found a slight reduction in certain acute and chronic infections. Davison¹⁵ mentions the common occurrence of edema as a complication in protracted cases of dysentery while Fröhlich and Gozsy¹⁶ emphasize the decrease in the albumin fraction in this disease. Some investigators¹³ have noted a decrease in serum albumin in seurvy while others have failed to find such a change.¹† Although figures for serum proteins are generally not given, the nutritional disturbance associated with celiac disease has been described as frequently complicated by edema which is considered similar to war edema.¹६, ¹⁰

The results of many studies are confusing because the attempt is made to associate changes in serum protein with a given disease irrespective of the state of nutrition or degree of hydration of the patients studied. The use of a wide variety of analytical methods has added further to the confusion. The literature as a whole is singularly lacking in any extensive study of the relation of serum proteins to malnutrition and edema in children.

# METHODS

In the work which we shall present here serum proteins were determined by the micro Kjeldahl method. All determinations were run in duplicate. Total protein was determined on 1 c.c. of a 1:10 dilution of serum representing 0.1 c.c. of the original serum. The phosphoric sulphuric-persulphate digestion described by Van

Slyke<sup>20</sup> was used. The nitrogen present was determined by distillation into 10 c.c. of N/50 HCl followed by titration with N/50 NaOH from an accurate buret. When sufficient material was available the nonprotein nitrogen was determined by the Polin-Wu procedure<sup>21</sup> and the value subtracted from the figure for total nitrogen obtained by the Kjeldahl method. In some instances the figures for total nitrogen were arbitrarily corrected by assuming the average value of 30 mg. of nonprotein nitrogen per 100 c.c. The protein nitrogen was converted to protein by the generally accepted factor 6.25.

The albumin and globulin were separated by Howe's method<sup>22</sup> of salting out globulin with sodium sulphate. The albumin nitrogen was determined in aliquots of the filtrate, corrected for N.P.N., and the nitrogen figure converted to protein as in the case of total protein. Globulin was invariably calculated by difference.

### OBSERVATIONS OF NUTRITIONAL EDEMA

Over a period of nine years we have collected forty-one cases of edema in which a thorough study of the patient revealed no evidence of cardiac or renal involvement. Sometimes the edema was confined to the feet and legs, but there were several instances of generalized anasarca. The condition was observed in children from four months to nine years of age. Five children of the group had no demonstrable disease other than generalized edema; nine either had, or were convalescent from, bacillary dysentery; ten had diarrhea with stools not typical of dysentery; three had pneumonia; two were diagnosed as having celiac disease; three showed evidence of scurvy. There was one case each in which edema complicated pellagra, typhoid fever, tuberculous enteritis, diabetes, and a common cold. Four children had histories of repeated infections.

The previous diet was known to be good in three cases: the child with tuberculous enteritis, a child with diarrhea, and one with a history of multiple infections. In most of the other instances the diet offered was grossly deficient or there had been a long period when the appetite was poor. Breast feeding had been continued long after the supply of milk was sufficient, and supplementary foods had not been offered or consisted of gravy, biscuits, corn bread, cereal and potatoes. The older children ate only potatoes, corn bread, turnip greens, and beans. In many instances the food was offered with no regularity, and no attempt was made to teach the child to eat or to see that he received an adequate amount of food. The child's apparent preference coupled with what was convenient was the only guide to the diet. Supplementary vitamins were almost never given. Occasionally the dietary history as obtained sounded far better than the condition of either the child or the mother made credible.

From our total of forty-one cases we are presenting in Table I twenty-six in which studies of the various fractions of serum protein were made. No case is included in which there was found more evidence of renal involvement than a slight elevation of N.P.N. or a transient trace of albumin in the urine, following a period of low fluid intake. A few

Table I Clinical and Chemical Data on Twenty-Six Children With Edema

								PER	PERCENTAGE OF	£ .
	-			HEMO-		HISTORY AND DURATION	EDENTA	SERI	SERUM PROFEIN	Z
GASE	NOE	W.	WEIGHT	GLOBIN	FEEDING	OF DISEASE		TOTAL /	VLBUMIN	TOTAL ALBUMIN GLOBULIN
,		5	5	GM.		C. 11 Lan 166 Dollagra	General	5.0	5.0	5.1
-	6 yr.	95	c	10.2	Breast fed 2 years, Sinco then diet mostly of fat ment and corn bread.	sickly all not tite. I carefice and edema for 6 months.				1
¢1	2 37.	16	15	9.1	Breast fed 1 year. No regular incals at present.	Poor health for 1 year. Edena for 7 months.	General	£.3	1.8	 
					Dict mostly soup and	Scurvy, general avitamistrosis.			•	ć
m	9 ma.	55	œ	11.0	Breast fed. Cerenl, bana- nas, and vegetables sinco	Well first 6 months. Tuber- culous enteritis.	Extremities	5.9	5) 51	3.0
					5 months.				1	
÷	6 mo.	21	G	3.3	Breast fed 4 months. Various whole-milk formulas	Acuto G.I. indigestion 2 weeks. Severe secondary anemia.	Extremities	ಸು ಬ	ట స	o. 1
က	19 mo.	1:	ب	9.8	Breast fed, with added cereal, crackers and bread.	Had fever 3 mouths before	General	44	₹. 61	0:1
						diarrhea.				
Ð	19 mo.	10	<del>-</del> #	7.5	Coreal, vegetables, meat, fruit, milk, eggs.	Diarrhen and vomiting 4 weeks; edema 1 week.	Genoral	4.6	2.7	1.0
1-	A G	61	w	8.1	Details unknown.	No disease. Edema 3 days.	Face, ascites	6.1	3.8	2:3
· თ		38	- च्यू	6.0	Breast fed. No supplemen-	History of multiple infec-	Slight	5.3	3.5	1.7
	•				tary food.	tions,	***************************************		***************************************	

TABLE I-CONT'D

CASE	NOE	WE LB.	WEIGHT LB.   02.	GLOBIN GM.	FDEDING	HISTORY AND DURATION OF DISEASE	EDEMA	PER	PERCENTAGE OF SERUM PROTEIN	F 8
-								TOTAL	TOTAL ALBUMIN GLOBULIN	GLOBULIN
<del>.</del> .	.,	ş	t-	10.2	Diet of turnip greens, potatoes, and ham sand- wiehes.	Multiple infections for 5 months,	General	<b>3</b>	-i	3.0
92	+ mo.	1~	×	9.3	Breast fed 2 months. Then rice water, white of egg, and Imperial Granum,	Diarrhea 2 weeks, Intermittent edema all his life,	Marked, general 3.7	al 3.7	÷ ci	1.3
Ξ	2 yr.	18	¢1	12.0	Brenst fed with added cow's milk, No other food,	Diarrhea 3 months, Edem 1 for some time.	PUM	5.1	3.2	6:1
23	19 mo.	36	9	9.0	Breast fed, with added butterm i Jk, vegetables, eereal, and fruit for last 7 months.	Diarrhea 3 weeks. Edema 3 weeks.	Matked, general 3.1	ıl 3.1	5.1	1.3
	21 mo.	Ξ	œ	12.8	Family very poor, Very little food available,	Vomiting and diarrhea 2 weeks	Moderate,	6.3	÷::	8:0
	2 yr.	<del>5</del> 1	<del></del>	9.6	Breast fed 10 months. Since then chiefly potatoes, some fat meat, and apples.	Вгопсьорпептопія З даув	general General	3.5	0.1 -4.	1.1
	yr.	13	-	8.8	Breust fed. Meat, egg, vegetables and milk for past year.	Diarrhea 1 month	Mild, of feet	4.7	1.9	& &i
16	6 mo.	13	9	4.6	Dilute skim-milk formula.	Diarrhea 1 month	Moderate,	4,3	3.2	1.1

ABLE I-CONT'D

CASE	AGE		WEIGHT LB.   OZ.	GALOBIN GAL	PEEDING	HISTORY AND DURATION OF DISEASE	EDEMA	SER TOTAL	PERCENTAGE OF SERUM PROTEIN L   MUBUMIN   GI	PERCENTAGE OF SERUM PROTEIN TOTAL ALBUMIN GLOBULIN
17	19 то,	#	=	8.9	Breast fed 14 months.	Dysentory 5 weeks	Extremities	4.3	S:	1.5
18	2 yr.	çi	œ	7.5	No details known.	Dysentery 8 months	Mild	4.7	3,4	1.3
19	1f mo.	. 11	10	11.4	Breast fed 13 months. Rice water, milk, and orange juice since.	Dysentery 2 months	Moderate, general	4.0	io ci	1.5
50	11 mo.	. 13	S	10.8	Breast fed 8 months. Since then oatmed, pot-liquor, potatoes, gravy, and bread. No milk.	Diarrhea 1 month previously. Edema since that time.	Marked, general 4.8	al 4.8	ci T	ci
ត	24 yr.	16	13	8.2	"Boarded out," Apparently starved for long time.	Starvation. Scurvy (?) Beriberi.	Marked, general 3.5	1 3.5	1.3	က င <b>်</b>
8]	9 mo.	19	C1	10.5	Whole milk and ecreal.	Multiple infections all his life.	Mild, extremities 4.8	s.4.s	6.5	1.9
ş	2 yr.	56	œ	8.6	Breast fed 1 year. Then meat, bread, potatoes, vegetables, and milk.	Pneumonia. Lung abscess 4 weeks.	Marked, extremities	6.4	L' Gi	3.7
ទីវិ	13 yr.	<b>6</b> 3	S	;	Breast fed 10 months. Mostly beans since.	Dysentery 2 weeks.	Marked, extremities	5.3	3.5	1.8
	5} yr.		51	13.2	On celiac diet 4 months. On general diet 1 month.	Severe diarrhen. Celiac discase.	Marked, extremities	s;	1,4	1.4
0.7	9 yr.	#	oc	8.6	Poor "general diet."	Celine disease.	Extremities	3.5	1.9	1.6

children had been reduced to a state of cachexia by prolonged starvation or disease; two had celiac disease; one had no apparent disease. The majority were children who were poorly developed and undernourished but not critically ill, in whom a mild, acute or chronic diarrhea apparently brought out a latent edema. The levels of hemoglobin observed in the group of children give further evidence of their poor nutritional state. The photograph (Fig. 1) illustrates a typical case. From Table I it is apparent that in every case the levels of total



Fig. 1.—Photograph of child presenting a typical picture of nutritional edema.

protein and serum albumin are lower than any generally accepted range of normals. The most marked reduction is in the albumin fraction. Occasionally the globulm is reduced but in a majority of instances is normal or increased above the average.

In order to bring out more clearly the variation of these figures from the normal the data are presented graphically in Fig. 2. The cases are divided into two groups, the figures for the children under two years of age being charted separately from those of the older group. Each horizontal space represents an individual. The albumin fractions are arranged in ascending order of magnitude. Under each figure for albumin is charted the level of globulin and total protein of the same serum. The horizontal dotted lines drawn across the charts represent the normal level of the various types of protein for the two age groups. These normal levels are, of course, only approximate but are drawn at the average normal level as determined by our work to be published in

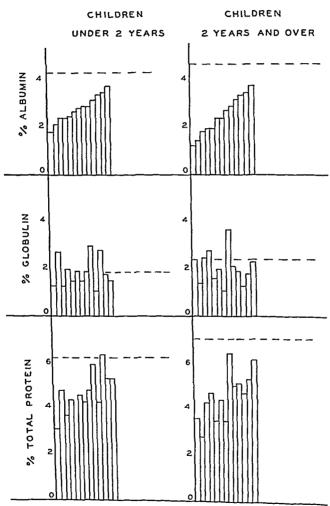


Fig. 2.—Graphic representation of levels of total protein, albumin and globulin of patients with edema. Dotted line indicates approximate normal level.

another paper. Our average normal is about the same as that published by other investigators.

In most instances treatment of the primary disease together with a high protein diet and transfusions of blood, when necessary, brought about a prompt reduction of edema followed by a gain in real weight and recovery. Determinations of serum proteins during the recovery period showed a gradual increase to normal levels. In one instance, Case 21 in Table I, the circulatory collapse was so marked on admission and the serum albumin was so low that acacia solution was given intravenously in order to restore a more efficient oncotic pressure to the blood more rapidly than could be accomplished by other means. Sometimes the nature of the primary disease precluded any real improvement, or death resulted from intercurrent infection. In cases in which the edema was associated with the nonspecific type of diarrhea, it was interesting to note that as the serum proteins were raised to a more normal level and the edema disappeared, the diarrhea also subsided. This observation throws some doubt on which is primary and which secondary when nonspecific diarrhea and nutritional edema occur together in infants and children.

The two following protocols are included to show more in detail the course of recovery and restoration of normal serum proteins in two children who responded rapidly to treatment.

Case 2.—(Table I.) R. L. G., white, female, aged two years, entered the hospital Oct. 3, 1934, with the complaint of being "swollen all over." The child had been breast fed for one year without supplementary foods or cod liver oil or orange juice. Since weaning she had received no regular meals but had nibbled at food throughout the day. Her diet consisted of soup, gravy, bread, potatoes, and salt meat with a little milk occasionally. Recently she had received large quantities of a tea made of watermelon and broom corn seeds. There had been no illnesses other than the present condition. Seven months before admission the feet and ankles began to swell and generalized edema gradually developed. The edema was intermittent but never was absent for more than a few days. Periods of anuria had occurred sometimes lasting as long as twenty-four hours. There had been no other urinary symptoms. Physical examination showed an undernourished, underdeveloped, pale child with marked edema of the legs, arms, and face. The serum proteins on admission were total protein, 4.3 per cent; serum albumin, 1.8 per cent; and serum globulin, 2.5 per cent. The urine was entirely negative.

The child was placed on a high protein diet which she ate well. In addition, a transfusion of 170 c.c. of blood was given. She lost two pounds during the first five days in the hospital; the edema disappeared; and a mild diarrhea, which had been present, subsided. Five days after admission, on Oct. 8, 1933, the serum proteins were: total protein, 4.9 per cent; albumin, 2.0 per cent; and globulin, 2.8 per cent. The child continued to cat well and to gain weight.

On Oct. 18, 1934, the serum proteins had risen to total protein, 6.7 per cent; albumin, 3.4 per cent; and globulin, 3.3 per cent. The child has been followed in the out-patient department and on an adequate diet has continued to do well. There has been no reappearance of edema.

Case 6.—(Table I.) C. II. G., white, male, aged nineteen months, entered the hospital Oct. 28, 1930, with the complaint of diarrhea and vomiting of one month's duration. The child was supposed to have been well fed on a diet of cereals, bacon, fruit, vegetables, and milk, with an occasional egg, but the appetite had been very poor since the onset of the present illness. There was well-marked edema of the feet and legs. The serum proteins on admission were total protein, 4.6 per cent; albumin, 2.7 per cent; and globulin, 1.9 per cent. The urine was normal.

The child was put on a diet of whole milk for the first day or two and then on a regular soft diet which is moderately high in protein. The edema disappeared

during the first four days in the hospital. There was a weight loss of 15 pounds during this period and then the child began to gain. On Nov. 5, 1930, eight days after admission, the seium proteins were total protein, 6.0 per cent; albumin, 3.9 per cent; and globulin, 21 per cent The patient gained 3 pounds in about two weeks in the hospital and has done very well since.

### DISCUSSION AND SUMMARY

This study shows that generalized edema of neither cardiac nor renal origin may occur fairly often in infancy and childhood of edema is most characteristically associated with malnutration. The poor state of nutrition may result from chronic gastrointestinal disturbances, such as celiac disease, protracted dysentery, or tuberculous enteritis. Repeated or prolonged infection may also be a factor in its production. In the dispensary group in this locality the most common underlying cause of this type of edema is a diet which is grossly inadequate in total calories and in protein, either because of ignorance on the part of the parents or because of economic stress. A common factor in the condition, whatever the cause, is a marked decrease of serum protein, especially of the albumin fraction. Unless the primary disease is of a nature to preclude recovery, treatment with an adequate diet. sometimes supplemented by transfusions of blood, results in a restoration of normal serum proteins and a prompt reduction of the edema.

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# THE OCCURRENCE OF MODERATELY REDUCED SERUM ALBUMIN IN FIVE HUNDRED CHILDREN IN A SOUTHERN CLINIC

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IN ANOTHER communication we reported the occurrence of edema of neither cardiac nor renal origin in our group of clinic patients. Every instance of edema was associated with a marked reduction of plasma protein, especially of the albumin fraction. The hypoproteinemia was due primarily to malnutrition, although in some instances acute or chronic infections and gastrointestinal disease were undoubtedly contributory factors.

During the same interval that these observations were made, we noticed that many children who entered the hospital with acute diseases tended to develop edema very easily when moderate amounts of parenteral fluids were given. It seemed possible that many of the children in the clinic group, when they were apparently well, might have milder degrees of the same nutritional deficiency which had led to outspoken edema in the instances already reported. If such were the case, the nutritional disturbance would be analogous to subclinical vitamin deficiency. We therefore determined the serum protein levels of 500 children who came to our clinic. For comparison with these results a smaller group of well children of various ages who were known to be on adequate diets were similarly studied. The results of the studies are presented in this paper.

Our clinic is limited to children whose parents are unable to pay a private physician. The ratio of white to colored patients is about three to one. The infants who are fed under our supervision or that of one of the well baby clinics are usually well nourished. There are also many well-fed older children, but undersized and poorly nourished individuals are common. During the period of this investigation many of the families were out of work and supported by relief. Although the amount of money received by the families on relief was usually low, sometimes not more than three dollars a week for a family of four, often as much was spent for food as when the parents were employed. The depression undoubtedly contributed somewhat to the inadequacy of the food of many of the patients, but a more prolonged poor economic status and the dietary habits of the community are probably more important factors. Both older children and infants are often fed similarly to the children

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with nutritional edema whose cases were reported in our first paper. The dietary, as Youmans<sup>2</sup> has described for adults with edema, is often inadequate in protein and in total calories.

The blood for serum protein determinations on both normal and clinic children was taken without regard to activity or the interval after a meal. No rest period before the sample was taken was given to the older children who were well enough to walk into the clinic. The smaller infants and the sick children had, for the most part, been in a recumbent position for some time before the sample was taken. We realize that a uniform procedure under basal conditions would have given us more exactly comparable figures, but facilities were not available for such a study. All determinations of serum protein were made by the micro-Kjeldahl method as described in the preceding paper.

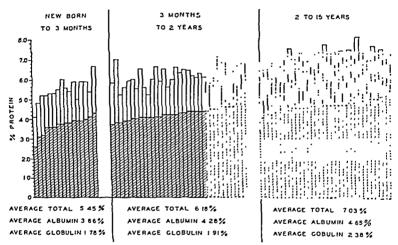


Fig. 1.—Levels of serum proteins in normal well-nourished children of various age groups.

# SERUM PROTEIN LEVELS OF NORMAL WELL-NOURISHED CHILDREN

In order to evaluate the results obtained in the clinic group it was necessary to study the serum proteins of healthy, well-fed children throughout the range of pediatric age by the same chemical methods and under the same conditions. We found, as has already been shown by others, that small infants have a low concentration of serum proteins and that the level gradually rises as the child grows older, to reach the adult level at about two years of age. After two years no consistent variations were found. We therefore divided the normal children into three age groups: (1) newborn to three months; (2) three months to two years; (3) two to fifteen years. The results obtained are presented graphically in Fig. 1. Each horizontal space represents an individual. The height of the column represents the total serum protein, the crosshatched portion the albumin, and the clear space above, the proportion of globulin. A

gradual increase in both fractions of the protein may be noted as the age increases. The averages obtained for the younger infants are in general like those reported by Darrow and Cary<sup>3</sup> although our small series shows less evidence of a high albumin-globulin ratio than they found. The figures obtained in the older infants are distinctly lower than adult levels but higher than those of the younger infants. The average obtained in the group of children from two to fifteen years of age is in accord with the usually accepted normal average for adults.

### SERUM PROTEIN LEVELS OF THE CLINIC GROUP

The children studied were divided into the same age groups as the normals. Too few figures on individuals under three months were obtained to be of any significance, and they are not presented here. As disease is known to influence the levels of serum protein, the age groups

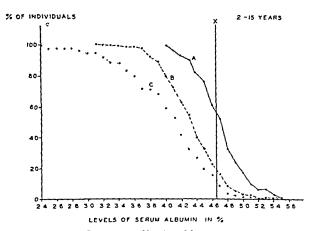


Fig. 2.—Ogive (cumulated downward). Graphic representation of distribution of serum albumin levels in children two to fifteen years of age.

Group A, 33 normal well-nourished children; Group B, 227 clinic patients not ill. Group C, 64 clinic patients ill. Line X indicates average normal level.

are subdivided into siek children, nearly all of whom had acute or chronic infections, and children with no significant active disease. Only the figures for the albumin fraction of the scrum protein were used in making the charts because this fraction has been shown to be the most important in maintaining fluid relationships and is, as well, the first to be reduced by malnutrition and disease. For convenience in discussing the results, the normal group of children in both age groups will in the future be spoken of as Group A, the clinic children without significant disease as Group B, and the group containing those with acute or chronic infections as Group C.

Figure 2 is a graphic representation of the serum albumin percentages of the children from two to fifteen years of age in the form of ogives. Along the ordinates are plotted the percentages of the group having an

albumin level above that indicated by the figures on the abscissa (cumulated downward). The solid line is the curve for the albumin of thirty-three individuals in Group A, and serves as a basis of comparison with the other groups. The line of dashes represents the albumin figures of the 297 children in Group B, while the dotted line represents those of the sixty-four children of Group C. A perpendicular line is drawn through the curves at the average normal level. There is a distinct tendency for the curves of Groups B and C to run under that of Group A. Whereas 56 per cent of Group A reach or exceed the average normal

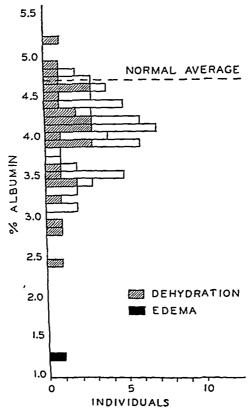


Fig. 3.—Graphic representation of distribution of levels of serum albumin in Group C, aged two to fifteen years, to show incidence of dehydration and edema.

level of albumin, only 20 per cent of Group B and 12 per cent of Group C attain this level. Ten per cent of Group B and 32 per cent of Group C have albumin levels below the lowest figure found in Group A. Many of the children of Group C were dehydrated at the time the sample of blood was taken. This factor would tend to concentrate the serum proteins. Figure 3 is a graphic representation of the albumin levels of the individuals in this group to show the incidence of dehydration.

The results obtained in the age group from three months to two years are presented according to the same plan as those obtained in the older

group. The ogives represent the figures on thirty-four individuals of Group A, fifty-seven of Group B, and forty-one of Group C. At this age the curves of Groups A and B were practically identical. This is at first surprising in view of the results obtained in the older group. On further analysis it was found that the majority of infants who came to our dispensary without a serious illness are those who are being fed under our direction. Thus, although the individuals are unselected as far as this study is concerned, they are probably not a fair sample of the general local clinic population of this age. Either the mothers who feed their infants badly do not seek advice until some acute illness occurs, or the poorly nourished children pick up infection easily. There are many poorly nourished infants in our dispensary, but they are almost all ill. Again, in this age group the albumin levels of Group C run well below both the lower limit of normal and the average of Group A. In order to

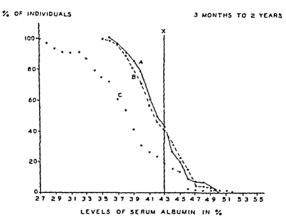


Fig. 4.—Ogive (cumulated downward). Graphic representation of the distribution of serum albumin levels in children from three months to two years of age.

Group A. 34 normal well-nourished children; Group B, 57 clinic patients not ill; Group C, 41 clinic patients Ill. Line X indicates average normal level.

show the incidence of dehydration in Group C, the results are also shown in Fig. 5. It may be noted that practically every figure which is at or above the normal average was obtained on a dehydrated infant.

A few of the individuals in our clinic group, as may be noted in Figs. 3 and 5, had edema at the time the blood samples were taken. A good many others had concentrations of serum albumin which are at or near the level at which edema often appears. When these children were acutely ill and were given even moderate amounts of subcutaneous saline on admission to the hospital, they often became edematous. In the younger children edema commonly appeared when, because of diarrhea, food and fluid were discontinued by mouth and intravenous and subcutaneous fluids were used instead. One child with celiac disease, whose serum albumin level in spite of marked dehydration was 1.4 per cent on admission, developed a mediastinal effusion when she was

given subcutaneous saline. Another child developed a generalized edema with free fluid in the pleural, pericardial, and peritoneal cavities. We find that we have been obliged to grow more and more conservative about the administration of parenteral fluids, especially saline, and that we must constantly be on the lookout for edema.

We realize that decreased serum protein percentages are not the only factor concerned in the appearance of edema in sick children, even when they have neither cardiac nor renal disease. The intake of salt and water has a great influence on whether or not edema appears at a given degree of hypoproteinemia. Vitamin deficiencies, lack of calcium, and infections all increase the permeability of the blood vessels. We believe, however, that our findings indicate that we are dealing in our

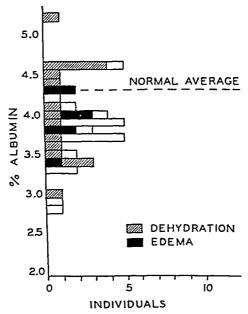


Fig. 5.—Graphic representation of distribution of levels of serum albumin in Group C, aged three months to two years, to show incidence of dehydration and edema.

elinic group with many individuals who already have a hypoproteinemia due to malnutrition and that they develop edema much more easily than normal individuals.

It was hoped that further division of the data according to race, details obtained as to dict, or percentage above or below average normal weight might show more clearly the relation of the diet to the hypoproteinemia. No difference was found between the white and colored children. No marked difference was shown when we divided the children into groups according to whether the dietary history that we could obtain at a single visit sounded reasonably adequate or inadequate. The factor of blood volume which we hope to investigate later may largely explain the lack of conformity between the serum protein levels and the

weights of the children. One response to low protein diets or to depletion of plasma proteins by plasmapheresis in experimental animals is a considerable reduction in plasma volume.4 This may occur without a significant change in the concentration of plasma proteins, although the total amount of circulating proteins is thereby considerably decreased. If a similar response is made by children on a deficient protein intake, it may explain the finding of normal scrum protein levels in some greatly undernourished individuals

### SUMMARY AND CONCLUSIONS

We have presented the results of serum protein determinations in normal children of various age groups. These figures confirm the observations of others that the scrum proteins of infants are low and increase gradually to approximately the adult level at two years of age. The general level of serum albumin of our clinic group, even in the absence of acute or chronic illness, is somewhat below that of the normal group. The serum albumin in children with acute or chronic infection rarely reaches the normal average except in the presence of dehydration. A few of the children studied had edema when first seen. Several of the sick and dehydrated children developed edema following the administration of moderate amounts of parenteral saline. This work indicates that a chronic low grade deficiency in serum proteins is common among the poorer children in the community. The diet which is low in total calories and in protein is probably the cause of the deficiency. Such children are predisposed toward the development of edema, especially in the presence of infection.

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# SEASONAL VARIATION OF THE BIRTH WEIGHT OF THE NEWBORN

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SINCE Pastor Malling-Hansen (1883) of Copenhagen reported his observations on the periodicity in the gain of weight among children, various individuals, namely, Camerer and Amburg (1912), Bleyer (1917), Porter (1920), Emerson (1927), and others have followed in the same line of research. These workers, though not certain of the cause, came practically to the same conclusion that the growth in weight is accelerated from midsummer to fall and retarded in late winter and spring. This has stimulated the interest of some investigators in finding out whether similar seasonal variations of birth weight occur.

The first study of this kind was made by Adersen (1899). He examined the records of the birth weight and birth length of 2,960 infants born in Stockholm and found that newborn infants were larger in the first (colder) part of the year than those of the succeeding months. Hansen (1913) in his study of birth weight of nearly 6,000 infants of the Nykobing-on-Sealand District of Denmark, observed that infants born in the fall months were heavier than those born in the spring. Abels (1922) studied the birth weights of infants in Vienna. There were 1,166 infants in 1920, and 1,622 in 1921. found a rise of birth weight from March or April which reached a maximum in August and a minimum in the winter months. plained this as due to lack of the fat-soluble vitamin A, as during those postwar years people could not afford a sufficient supply of milk. butter, green fruits, or meat in winter. Katz and König (1923) tried to confirm Abels' observations and studied the birth weight of 14,425 infants in Germany; 7,484 of these were born in the years 1910, 1911, 1912, and the remaining 6,941 from the war and postwar years, 1917 to 1920. They combined the figures in the three prewar years to form one group and the four late-war and postwar years into another in order that the effect of change of nutrition in these two periods upon the birth weight might be studied. They found that the birth weight during the war and postwar years was in general below that of the prewar years, and there were small negative monthly fluctuations of the birth weight, but they were unable to say whether these negative fluctuations were due to lack of vitamins in the food. With a view to

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confirming the observations of Abels, Schlossmann (1923) studied the birth weights of 13.805 infants born in the years 1905 to 1922. He was unable to find a diminution in the birth weight in the winter months. Murray (1924) found that infants born in August, 1918 (59 cases), had the greatest birth weight (7.31 pounds), while those born in February of the same year (38 cases) had the lowest (6.78 pounds). There appeared to be a slight falling off in weight in march, which might indicate the unfavorable effect of cold weather during the last three months of pregnancy, but the range was not great, and the question required further study. Dunkin and others (1930) studied the seasonal variation of the birth weights of guinea pigs and found that, in general, albino guinea pigs born in the January-March quarter were below the average in weight and that those born in August and September were above the average; but these observations were not consistent, especially in the case of mixed color families.

Thus far, opinions differ with regard to the seasonal variation in birth weight. Adersen found a greater birth weight in the first half of the year. Hausen, Abels, and Murray found an increase in birth weight in the late summer and early autumn months. Katz, König, and Schlossmann found no definite difference. Dunkin and others found a greater birth weight in some series of guinea pigs during August and September and smaller birth weight in the January-March quarter. The present study is an attempt to ascertain, using some well-known statistical methods of analysis, whether seasonal variation of the birth weight of babies does exist.

The present study consists of two parts: (A) study of data of the Peiping Union Medical College Hospital, and (B) a collective study of available data in the medical literature.

# STUDY OF DATA FROM THE PEIPING UNION MEDICAL COLLEGE HOSPITAL

During a period of eight years and four months ending in June, 1930, there were 1,938 obstetric admissions to the Peiping Union Medical College Hospital. The number includes mothers of different nationalities, of various economic status, as well as in various medical conditions. On admission, the patient's name, age, address, occupation, nationality, and nativity were recorded. As a hospital routine, the record of present illness, marital and obstetric histories, and findings from a complete physical examination were required of every patient. The whole labor process and the condition of the infant were also recorded. Illegitimate births were also noted as such.

The temperature in Peiping in the cold months differs significantly from that in the hot months. The cold season begins about the first of November and ends by about the middle of March. The average winter temperature is about 10° F. above zero but the lowest temperature may be as low as 20° F. below zero. The hot season begins

about the middle of June and ends about the middle of September. The average temperature in the summer is about 90° F., but may be as high as 105° F. The months from the middle of September to the end of October and from the middle of March to the middle of June are very temperate. The Peiping weather is quite similar to that of Boston, except that the former is not so humidas that of the latter.

Li (1928), in a study of factors affecting the birth weight of the newborn, found that birth weight undergoes a considerable amount of normal variation, and that it is affected by such factors as nationality, sex, duration of gestation, birth order, multiple pregnancy, size of mother, and health of mother; age of mother under twenty years possibly also exerts an unfavorable effect. In order to avoid the concealed influences of these factors, care is given in the present study to the statistical analysis. Only infants of Chinese parentage are used: all premature births, stillbirths, illegitimate births, and multiple pregnancies are excluded; mothers or infants suffering from tuberculosis, heart disease, eclampsia, syphilis, or pneumonia are not included, though patients suffering from diseases of mild character or short duration such as headache, acute dysentery or diarrhea and surgical conditions are retained. The number thus excluded is 890 cases, leaving a total of 1,148 selected cases of Chinese parentage. sample is furthermore studied with regard to the age of the mother. nativity of the mother, sex of the infant, its month of birth, order of birth, and birth weight. The nativity of the mother is arbitrarily divided into three groups: the southern, the central, and the northern. Fukien, Kwangtung, Kwangsi, Yunnan, Kweichow, and Hunan provinces belong to the southern group; Szechuan, Hupeh, Kiangsi, Anhuei. Kiangsu, and Chekiang, to the central group; Shantung, Honan, Shensi, Shansi, Kansu, and those provinces north of them, to the northern group. The nativity of the father is not recorded; its omission is probably not important, because the Chinese mother's nativity is usually the same as the father's as she is customarily married to a man of her native province.

Each monthly sample is thus analyzed with respect to possible influence exerted by such factor as mother's age, nativity of mother, sex, and order of birth (Table I); the distribution of these factors throughout the sample is fairly even in all months and they exert no significant influence in the conclusions to be drawn from the data.

The result of this study shows that the monthly means undergo some fluctuation (Table II). The lowest mean occurs in February (2907  $\pm$  44 gm.), while the highest is in July (3185  $\pm$  68 gm.); the difference between these two extreme values is 278  $\pm$  81 gm., which is significant. A closer observation of the whole series of the monthly averages reveals, however, that there seem to exist a decrease in birth weight

TABLE I

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MONTH OF BIRTH	NUMBER CASES	BIRTH WEIGHT (GRAMS)
January	99	2,967 ± 37
February	91	$2,907 \pm 44$
March	100	$2,965 \pm 43$
April	100	$3,058 \pm 39$
May	101	3,133 ± 36
June	81	$3,029 \pm 58$
July	86	$3,185 \pm 68$
August	96	$3,094 \pm 71$
September	100	3,045 ± 40
October	100	$3,060 \pm 48$
November	85	$3,077 \pm 49$
December	109	3,053 ± 48

1,148

TABLE II

MEAN BIRTH WEIGHT OF CHINESE INFANTS BY MONTH OF BIRTH

during the winter months and an increase during the summer months. To confirm this a statistical test was made. The cases were distributed or redistributed according to their month of birth into six groups as follows: Group I, births occurring in December, January, and February (the cold months); Group II, births occurring in October, November, and March (the temperate months); Group III, births occurring in April, May, and June (the fairly warm months); Group IV, births occurring in July, August, and September (the hot months); Group V, births occurring from April to September (the warmer half of year), and Group VI, births occurring from October to March (the colder half of the year). These are given in Table III.

The mean birth weight of these six groups indicates the existence of the lowest birth weight in the cold months which increases as the warm weather advances, reaching its maximum during the hot months. The difference between the mean birth weight of Group I and that of Group IV is  $165 \pm 29$  gm. and is very significant, the difference between that of Group V and that of Group VI is  $106 \pm 18$  gm. and is also very significant.

A general glance at Table III reveals certain differences in the way in which the birth weights of each of the six groups are distributed; more cases of light weight occur in the cold months than in the warm months. It remains for one to take the distribution by weight of any group in Table III and compare it with the distribution by weight of any other group by the use of  $\chi^2$  test in order to find out whether the distributions of these two groups are significantly different from each other.\* The following results are given in Table IV.

The inference drawn in the  $\chi^2$  tests is that the distribution of birth weights of infants born in the cold months is significantly different from the distribution of birth weights of infants born in the warm months, as well as that the distribution of birth weights of cases born

<sup>\*</sup>For readers who wish to know detailed procedures in applying the Chi-Square Test, Pearl's Medical Biometry and Statistics, ed. 2. Chapter XII, pp. 315-326, may be

Table III

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in temperate months (Group II) is not significantly different from the distribution of the birth weights of cases born in months the temperature of which is not much dissimilar (Group III). This leads to the same conclusion that there exists a real difference in birth weight with respect to season.

Table IV  $\chi^2 \ \text{Test for Significance in Difference of Distribution by Weight of Various Groups}$ 

χ <sup>2</sup> TEST FOR DIFFERENCE IN DISTRIBUTION BY WEIGHT BETWEEN	VALUE FOR $\chi^2$	VALUE FOR P.	INFERENCE
Group I (Dec., Jan., Feb.) and Group IV (July, Aug., Sept.)	26.6866	0.005	Significantly different
Group V (April-Sept.) and Group VI (OctMarch)	20.9154	0.033	Quite significantly different
Group II (Oct., Nov., March) and Group III (Apr., May, June)	13.5022	0.26	Not significantly different

### COLLECTIVE STUDY OF DATA FROM VARIOUS SOURCES

An attempt is made to utilize, in addition to the data given above, samples published by other investigators. Only samples having a minimum of 1,000 infants are chosen. Accordingly, nine sets of data published by six investigators are selected: namely, two sets presented by Abels (1922), two sets by Katz and König (1923), a set by Schlossmann (1923), two sets by Momm (1916), and two sets by Ruge (1916). The first five sets were used by their respective investigators for the study of seasonal variation in birth weight. The last four sets were used by their investigators for study of the effect of poor nutrition upon birth weight, but they can be utilized here for the study of seasonal variation. These give a total of ten sets of data as tabulated in Table V.

Fluctuations in the monthly averages are present in all sets. A reduction in weight during the winter months is observable in most cases. The following plan is adopted to find out whether any uniformity exists in seasonal fluctuation of birth weight. Each set is taken separately; each monthly average is compared with the respective yearly average; if the former is greater than the latter, a plus sign (+) is given; if smaller, a minus sign (-), disregarding the magnitude of such differences. The results, given in Table VI, show a predominance of minus signs during the cold months and of plus signs during the warm months.

TABLE V
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TABLE VI

MONTHLY MEAN BIRTH WEIGHTS ACCORDING TO THEIR RESPECTIVE YEARLY AVERAGES, PLUS SIGN INDICATION OVER THE YEARLY AVERAGE AND MINUS SIGN INDICATING THE OPPOSITE CONDITION

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Now, the question is this: Can the predominance of minus signs during the cold months or that of plus signs during the warm months be explained by the matter of chance variation? In order to answer this question, the months of birth are grouped into six groups as previously; the plus signs and minus signs belonging to each group are summed; two groups are taken at a time and subjected to the  $\chi^2$  test; the results are given in Table VII.

TABLE VII

TEST FOR SIGNIFICANCE IN DIFFERENCE IN DISTRIBUTION OF THE PLUS AND MINUS SIGNS AMONG VARIOUS GROUPS

GROUPS	+	_	TOTAL	
V. April, May, June, July, Aug, Sept. VI. Oct., Nov., Dec., Jan.,	42	18	60	$\chi^2 = 3.463$ $P = 0.0004$ Inference: Difference is
Feb., March	23	37	60	very significant
Total	65	55	120	
I. Dec., Jan., Feb.	8	22	30	$\chi^2 \equiv 5.983$
IV. July, Aug., Sept.	25	5	30	P = 0.0000
Total	33	27	60	Inference: Difference is
				very significant
II. Oct., Nov., March	15	15	30	$\chi^2 = 0.578$ P = 0.95
III. April, May, June	17	13	30	
Total	32	28	60	Inference: No difference

These results indicate that the prevalence of lower monthly averages than the yearly average in the cold months and the opposite condition in the warm months cannot be explained by the matter of chance; and this supports the findings of smaller birth weight in the cold months and a greater birth weight in the warm months.

## DISCUSSION

The study of seasonal variation of birth weight is not a new one. The present findings are similar to those of Hausen, Abels, and Murray. The reason for lack of uniformity in the results obtained by all of the previous workers is probably due to nonappliance of statistical procedures; the normal variation of birth weight itself is large; and results are thus hard to be drawn without statistical considerations. Besides, there are so many other factors which may exert concealed influences in the averages and which should be carefully ruled out before inference can be drawn.

S. W. Li (1930) studied the birth weight of practically the same sample of Chinese babies born in the Peiping Union Medical College Hospital and found that male babies weighed more than the female, the average weights being 3,124 gm. and 2,980 gm., respectively, with a difference of 144 gm. According to Table III, the difference between the mean birth weight of babies born in the warm months (Group IV) and that in the cold months (Group I) is  $165 \pm 29$  gm. and is probably somewhat greater than the difference due to sex.

It is interesting to note that seasonal variations of birth weight are in agreement with those of the growth of the school children. would also be interesting to make further study of the birth weights in places where seasonal changes in temperature are negligible. is possible that, in these places, the seasonal variation of birth weight does not exist; and if it is so, it may be one of the causes for the discrepancy which previous investigators had brought out.

#### SHIMMARY

- 1. A statistical study of seasonal variation of birth weight has been made, using data collected from the Peiping Union Medical College Hospital and published statistics.
- 2. The present study shows the existence of a reduction in birth weight in the winter and early spring months and an increase in the late summer and early autumn months.

I wish to thank Dr. I. C. Yuan for many valuable suggestions in this study.

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# THE PROPHYLAXIS OF ALLERGIC DISEASE

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ROWE! has made the statement that allergy, next to infection, is probably the most important single etiologic agent in human symptomatology. If this statement is correct, the importance of prophylactic measures in allergic disease is easily understood. Since the fundamental constitutional abnormality which makes an individual susceptible to allergic disease is unknown, a completely rational system of prophylaxis cannot be advanced. Nevertheless, certain facts are known, and theories have been brought forward which deserve consideration in the study of this problem. It is rather remarkable that but one paper, that of Peshkin,2 has been published on this subject. The reason is perhaps that the problems in allergy have been and still are mainly those of finding the allergens responsible for disease in individual cases, and the treatment of disease from that standpoint. The purpose of this communication is to emphasize again some of the facts brought out by Peshkin and to add to these observations made since his paper was published.

Based upon our present knowledge, probably the first step in prophylaxis is the avoidance of marriage between allergic individuals. Of the few fundamental facts known concerning allergic disease, none is more firmly established than the fact of the inheritance of the allergic constitution. Vaughan' has pointed out that when the inheritance is unilateral, about 30 per cent of the offspring develop allergic symptoms during the first ten years of life. When the inheritance is bilateral, about 90 per cent of the children develop allergic disease during the first decade. Naturally this does not mean that in every case the allergic disease will be of a disabling nature; the symptoms may be only a transient eezema or eroup in infancy or a mild case of pollenosis in one of the children. On the other hand, no practicing allergist can fail to he impressed by the tragedy of a situation in which one of the parents may be disabled by asthma, for example, and all of the offspring afflieted with severe forms of eczema, urticaria, or asthma. The suffering involved and the economic and psychic strain placed upon the family may be very real and serious. Before a marriage is undertaken between allergic individuals it is only fair, if children are desired, for the wellinformed physician to explain the facts to one or both of the contracting parties so that they may decide whether or not the gamble is worth while.

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The next most important step in the prophylaxis of allergic disease is the careful observance of the diet of the pregnant mother in a family in which there are allergic diseases in the ascendants of the expected child. The basis of this is largely conjecture from animal experimentation, mainly the work of Ratner and his associates on the active and passive sensitization of guinea pigs in utero. Reasoning from these experiments, pica, the unnatural craving of the pregnant woman for specific articles of diet which she may eat in large amounts, is to be avoided because of the possibility that the offspring may be sensitized to that particular food. Ratner has reported cases where this appeared to be a factor. The pregnant mother should doubtless, with the possible exception of egg, have a varied diet without emphasis upon any one particular article of food.

It is well known that the manifestations of allergic disease in infancy are principally those of food allergy. In the food allergy of infancy, egg plays a particularly significant rôle. According to Hill and Sulzberger,6 85 per cent of all infants who react with positive skin tests do so to egg. This is true regardless of the fact that the infants have never ingested egg and may have fed only on the bottle and thus, also, have not had an opportunity to become sensitized to egg protein as a result of the passing of that substance through the mother's breast milk. Sensitization to egg must, therefore, occur in utero, and the mechanism is probably similar to the production of intrauterine sensitivity in guinea pigs in the experiments of Ratner4 mentioned above. Hill and Sulzberger6 state that since egg albumen has the lowest coefficient of digestibility of any protein and is the one most easily absorbed into the blood in its natural state, the human fetus, therefore, has ample opportunity to become sensitized to egg in utero. It is well known clinically that when marked sensitivity to one antigen occurs, upon the exhibition of that antigen the protective mechanism is often broken down so that sensitization to other antigens may follow rapidly. Since this is true, it is theoretically possible that by avoiding sensitization of the fetus to egg, perhaps subsequent sensitization to other substances may be diminished, delayed, or aborted altogether. 'The obvious step, therefore, is for the prospective mother of the potentially allergic child to avoid egg in her diet. Since food sensitivity has a tendency to be inherited in a specific manner, i.e., children whose parents are sensitive to a particular food tend themselves to be sensitive to that food, the indication is to avoid during pregnancy those foods which have previously been responsible for allergic disease in the family. The degree to which egg and other foods should be avoided cannot be stated definitely in the present state of our knowledge, so probably it is better to err on the side of safety and omit the potentially dangerous foods altogether. Because of the clinical fact that antigens may be transmitted through the breast milk

to cause allergic disease in the nursing infant, what holds true for the diet of the mother during pregnancy should probably hold true while she is nursing her child.

Calcium has long been thought to play an important part in the mechanism of allergic reactions, although its use as a therapeutic agent in any form of allergic disease is almost uniformly disappointing. It is unnecessary to go into detail concerning calcium because for reasons other than those associated with allergy the fetus requires liberal supplies of calcium. This should be taken by the mother in the form of milk or, if this is contraindicated, in the form of one of the numerous compounds of calcium now available as a substitute for milk calcium. Adequate amounts of a reliable vitamin D preparation or the utilization of sunlight or ultraviolet radition should be employed to insure utilization of the calcium so ingested. If this is done, at least the theoretical needs of the infant for calcium as a prophylactic agent against allergic disease will be well provided.

The next steps in the prophylaxis of allergic disease lie in the hands of the pediatrician, having been passed to him, as has been outlined above, from the general medical adviser of the parents of the potentially allergic child through the medium of the obstetrician. In the history of the development of the modern knowledge of allergy, pediatricians have played an important part. The term allergy was invented by the Austrian pediatrician, von Pirquet; and Schloss, formerly professor of pediatrics at Cornell, gave tremendous impetus to the clinical study of allergy when he made the first skin tests for foods in 1912. The more recent contributions of Hill have carried on the interest of the pediatrician in this field.

The pediatrician should consider both the environment and food of the potentially allergic child. Too little attention has been paid to the factor of environment. The clothing of the potentially allergic child should consist almost exclusively of cotton goods. Theoretically, wool, because it is an epidermoid, should be avoided, but practically it seldom causes trouble, even in infants with the worst allergic antecedents, and may be considered fairly safe to use, though the knowledge of its potential danger should be kept in mind. The foregoing remarks apply only to wool cloth and not to wool in the form of fur, as a sheepskin coat or blanket. Pure linen may be used but is not popular on account of the expense of the better qualities. Silk should never be used in the clothing, bedding, or hangings of the room of a potentially allergic child as the experience of recent years has shown that it is a frequent and dangerous antigen. It is too often forgotten that silk is of animal epidermoid origin and like most epidermoids has a great sensitization potentiality. Feather pillows and hair mattresses are to be avoided in the prophylaxis of allergic disease. Too many eases of sensitivity to

these substances develop in later life to risk their presence when adequate substitutes as cotton or kapok or synthetic nonallergic materials are available.

Following the same line of reasoning fur-bearing or feather-bearing animal pets and furred toys are to be avoided in the environment of potentially allergic children. Dust sensitivity in childhood has been quite common in our experience, and while there is no way of escaping dust, dust-catching and dust-hiding furniture should be avoided, at least in the rooms of potentially allergic children. Toilet preparations containing orris root are not to be used because of the frequency with which sensitization occurs to that substance. Probably the safest preparations are those manufactured by several companies particularly for the use of allergic individuals. The use of dusting powders or insect exterminators containing pyrethrum is also bad practice because sensitivity to pyrethrum, a fairly close relative of the ragweed, is of frequent occurrence.

The pediatrician first comes into contact with food allergy ordinarily when the infant develops colic or eczema or both. While there can be no doubt that the symptom-complex of irritability, apparent peristaltic cramps, distention of the abdomen and eructations of gas, or the passage of excessive flatus, commonly called colic, can be due to causes other than allergy, careful observation will indicate that food allergy is responsible in many cases and deserves particular consideration in the potentially allergic child. The principal way in which colic is treated is by a change in the infant's diet which involves a modification of the ingested proteins. It is the opinion of the authors that food allergy is to a certain extent a natural physiologic phenomenon. This is suggested by the fact that as new foods are added to the infant's diet, an eosinophilia occurs which disappears as the infant becomes accustomed to the new food.7 It has been shown by Peshkin and Rost<sup>8</sup> that 10 per cent of normal children between the ages of two and fifteen years show positive or doubtful skin reactions which decrease as age advances, indicating, according to them, progressive desensitization. It is the inability of the potentially allergic child to make the adjustment to foods and other antigens which causes the appearance of symptoms which rise to a clinical level with the development of obvious allergic disease. In the potentially allergic infant, colic and eczema, even in their milder forms, are not to be lightly regarded because the child will "outgrow" the symptoms, as the physician commonly states. The potentially allergic child has a very real chance of developing intractable eczema or asthma. For this reason food modifications are to be employed early and with necessary frequency; the pediatrician should not hesitate to make radical changes to alleviate even mild symptoms of allergy in the potentially allergic infant,

According to the same line of reasoning, as with the avoidance of epidermoids, foods possessing a high degree of sensitizing power, such

as eggs, should be added very carefully to the diet and in small amounts. In the definitely allergic infant we do not as a rule introduce egg in the diet until the child is a year old, and then only with extreme care. It is our practice to accustom the potentially allergic infant gradually to egg by starting with minute amounts, as ½ teaspoon of a raw egg yolk mixed with the total day's formula of the three-month-old infant. If the child tolerates this small amount, the quantity of egg yolk is increased weekly until the child gets a whole raw yolk in his formula daily. Then egg white is added in a similar manner. The egg yolk contains the same proteins as the white, but in a much more diluted form, and by this procedure too much strain on the infant's protective mechanism may perhaps be avoided. The mother is warned to discontinue egg immediately if the child develops colic, a skin rash, or other untoward symptoms, as vomiting or diarrhea. Several months are allowed to elapse before egg is again added to the diet.

The addition of vitamin C to the infant's diet, particularly in bottlefed babies, is of paramount importance, the common practice being to supply this by means of orange or tomato juice. Allergy to these substances is more frequently manifested by belching or undue spitting up than by colic or a skin rash. If this is the case, the pediatrician may substitute pineapple or turnip juice in equivalent amounts to supply the necessary vitamin C. Turnip juice, while little used for infant feeding in this country, is employed to a considerable extent in Europe because of the greater expense of the other juices. In extreme cases we have resorted to the substitution of 20 mg. of cebione (ascorbic acid, Merek) daily to supply the necessary vitamin C instead of fruit or vegetable juice, apparently with good results. The cebione should not be added to the formula but should be given separately to avoid its destruction by oxidation, which occurs rapidly in water and more rapidly in milk, especially if the reaction is not acid. Cebione is also destroyed by boiling.

Allergy to cod liver oil is most unusual and has not occurred in our practice. Cases have been reported by Balyeat and Bowen; when this occurs vitamin A may be supplied by carotene in oil and vitamin D by viosterol. These substances we employ routinely in children who give positive skin tests to fish, although we have never noticed ill effects from cod liver oil in infants giving even extreme reactions to the cod fish protein test. The work originated by Hansen<sup>10</sup> showed there was a deficiency of unsaturated fatty acids in the blood of allergic eczematous infants. If this is found generally true of allergic infants, it suggests the addition of oils high in unsaturated fatty acids, as corn oil or linseed oil, to the diet of the potentially allergic infant. The application of this in such cases, however, awaits further investigation.

The diet of the potentially allergic child should be varied in order to avoid undue emphasis upon any one food. Cereals other than wheat should be used when possible because wheat will, in most cases, unavoidably form the bulk of the cereal taken in later life. As substitutes for wheat, rye, rice, oatmeal, corn meal and barley are available, and, if desired, sago, tapioca, and arrowroot. Buckwheat should be used sparingly as it has a high sensitization potentiality. The Irish and the sweet potato may also be classed as cereals. It is preferable to give the potentially allergic infant a single pure cereal instead of the proprietary mixtures of several cereals which are now on the market and are proving highly satisfactory in the feeding of the majority of nonallergic infants. By using single pure cereals instead of mixtures, the child's cereal diet may be easily changed from one to another, and the possibility of simultaneous multiple sensitization is avoided. In the same way it is preferable to start the infant on single vegetables rather than on a mixture such as is found in the usual vegetable soup. Later, when it has been determined which vegetables, cereals, and meats agree with the infant, the soup may be made from those ingredients. Fish must be added with extreme eare. We add minute amounts of canned tuna fish or salmon at about the ninth month once or twice a week, and stop these if allergic symptoms appear. We do not care to have our older children indulge in nuts, especially cocoanut and Brazil nuts, and also strawberries, and shellfish. Potentially allergic children should be careful to avoid overindulgence as the fresh vegetables and fruits appear each season because of the common occurrence of urticaria following their ingestion.

As the potentially allergic child develops, considerable attention should be paid to what the parents or even the physician may regard as food whims. That is to say, for no apparently valid reason the child may express a hearty dislike for some particular food which he is compelled to eat because "it is good for him." In the potentially allergic child these food dislikes often represent instinctive defensive reactions to foods which are actually or potentially harmful to the child. In practice this is borne out time after time when an allergic child reacts to those foods which a carefully taken history reveals he has always disliked. On the contrary, it must not be forgotten that a child may be very fond of some particular food to which he is highly sensitive. The important thing to remember is that there are few foods for which an adequate substitute cannot be found, and in the case of allergic or potentially allergic children who dislike particular foods, it is better to give the child the benefit of the doubt. Most of the relatively few problem children met with in our allergic practice have developed feeding problems because of the mistaken efforts of parents or physicians who were unwilling to do this or were uninformed upon this point.

The prophylaxis of allergic disease is important with respect to the procedures which pediatricians should take to protect the child from the usual contagious diseases. The prophylaxis of diphtheria by the use of the usual toxin-antitoxin mixtures, which unavoidably contain minute

amounts of horse serum protein, is to be particularly avoided and has never been practiced by us. Tuft<sup>11</sup> stated that about 28 per cent of children are sensitized to horse serum by this procedure, and that this is much more likely to occur in allergic children or children of allergic families. Perhaps this is one reason why allergic disease appears to be much more common now than it did when our parents were children. We formerly used, on the advice of Dr. I. Harrison Tumpeer, a special diphtheria toxin-antitoxin derived from sheep serum, sensitization to sheep serum being of comparatively little importance. Since toxoid for immunization against diphtheria was introduced, we have used only that product because as far as is known there is no danger of protein sensitization from that source.

Peshkin<sup>2</sup> pointed out that in a series of 100 cases of asthma in children ranging in age from six months to fourteen years, the attacks were initiated in 15 per cent of cases by pertussis, in 14 per cent by pneumonia, in 4 per cent by measles, and in 2 per cent by scarlet fever. Diphtheria and varicella were not observed to initiate the onset of asthma in a single case, which seems peculiar in view of the extensive use of diphtheria antiserum derived from horses. While the value of our latest prophylactic agents against whooping cough, namely the Sauer vaccine and the Krueger unaltered bacterial protein solution, is yet to be proved, personal experience since these were introduced leads us to believe that they have considerable merit and at least do no harm. We use the Sauer vaccine as a prophylactic at any age in the case of allergic children but with our potentially allergic children we have employed it only in infancy. Severe reactions to the vaccine are common in children over a year of age and are best avoided by discovering the child's tolerance by means of small initial doses.

As yet we have no adequate method for the prophylaxis of the various forms of pneumonia, but in allergic children who have had repeated attacks we have had occasional brilliant success by the employment of measures directed against the underlying allergy, as the elimination of, or treatment with, substances to which the child reacted and by the use of vaccines.

Measles is easily prevented or modified by the intramuscular injection of whole citrated blood, preferably from an older member of the family who has had measles. When we employ blood for such purposes, as well as transfusions for any purpose, we prefer to use the parent on whose side there is no history of allergy in order to avoid the possible passive sensitization of the recipient and the breaking down of his protective mechanism.

We do not attempt to immunize our infants actively against scarlet fever by means of the Dick treatments, as local experience has been unsatisfactory with this procedure. We prefer to protect our exposed children, potentially allergic and otherwise, passively by the intramuscular injection of human convalescent searlet fever serum, using pooled serum when available.

A simple procedure for active immunization against tetanus is highly to be desired. Perhaps it will not be long before a practical toxoid for this purpose will be available. The work of Bergy<sup>12</sup> and of Sneath and Kerslake<sup>12</sup> indicates that considerable progress has been made in that direction. The reason that this procedure is desirable is that there are at times, following an injury, few more perplexing problems than whether or not tetanus antitoxin should be administered. because the resulting serum reaction may be much more serious and cause much more disability than the original injury. Furthermore, many individuals suffering from severe allergic disease trace the onset of their condition to the injection of such serum. Their allergic balance has been so disturbed by the injection that they develop other allergic diseases following the original serum reaction. However, because of the serious results which might follow the development of tetanus, the physician has no choice but to administer antitoxin in case of reasonable doubt. For the past two years for this purpose we have used a preparation made from bovine instead of horse serum. Reactions occur, but they have not been nearly as frequent or severe as those following the usual antitoxin made from horse serum. If the bovine serum is used, there is a theoretical possibility of sensitizing a potentially allergic individual to lactalbumin, which is considered to be the same substance as serum albumin. Whether or not this will happen must be borne out by future experience.

As the potentially allergic child grows older, the allergy-minded pediatrician will watch carefully for the development of symptoms of pollenosis (rose or hay fever). If a child has a "summer cold" every year at the same time, the diagnosis is almost certain. It is not our practice, however, to treat such children until the diagnosis is obvious to the parents for the reason that without this their cooperation is difficult or impossible to secure. It is our practice with allergic children, regardless of the presenting complaint as eczema, asthma, or urticaria, to test routinely with ragweed and timothy pollen, in addition to the allergens usually indicated. We have observed the frequent occurrence of positive reactions to pollens in children who have never had pollenosis. In many of these children pollenosis has subsequently developed; and now because of this, if we give these children periodic injections of any kind for the presenting allergic complaint as, for example, the injection of house dust extract or vaccine for asthma, we also add the pollens to which the child reacts. We believe, although as yet we have no proof, that this may prevent the future development of pollenosis. That this is probably true is indicated by the recent work of Biederman.14 He found that of patients who react positively to pollens of one season and have symptoms, but who also have a skin sensitivity to pollens of an additional season,

approximately 5.5 per cent will develop symptoms to the latter the following year, and that patients hyposensitized against all important pollens to which they are skin sensitive remain symptom-free from the pollens to which there are added skin reactions.

The importance of repeated head colds as an allergic manifestation has been pointed out particularly by Cohen and Rudolph.15 The differential diagnosis between allergic corvza and infectious corvza is usually not difficult, particularly in children. For details of this, reference is made to their publication. If allergic coryga is successfully diagnosed and treated, its most common sequella, asthma, may perhaps be prevented. In this connection the question of the importance of tonsils and adenoids with respect to asthma and pollenosis is often asked. Bullen<sup>16</sup> has tersely summed up the situation in three sentences: Tonsillectomy does not aid in improving the results of treatment of nasal or pulmonary manifestations of allergy. Rare exceptions may occur. Nasal or pulmonary manifestations of allergy are as likely to occur in an individual whose tonsils have been removed as in one who retains his tonsils. these reasons, in our pediatric practice, we do not differentiate between our nonallergic, potentially allergic, or allergic children with regard to the indications for tonsillectomy and adenoidectomy.

In early childhood the pediatrician caring for the potentially allergic child should bear in mind the possibility that many diseases of obscure origin may possibly have an allergic basis. By detecting their origin early the possibility is presented of clearing up these diseases and preventing their development into more malignant forms of allergic disease. Childhood illnesses which may at times be on an allergic basis are anorexia nervosa, cyclic vomiting (perhaps a childhood form of migraine in which the abdominal instead of the cranial symptoms predominate), pylorospasm, chronic constipation or diarrhea, abdominal pain of obscure origin, enuresis, epilepsy, and perhaps many others. Because of the fundamental pathologic physiology of allergic disease, spasm of smooth muscle and edema, or both, and the number of tissues in which it is possible for these to occur, it is not surprising that almost any disease may be simulated by allergy.

In the field of sports the potentially allergic child deserves some consideration. If he rides or raises animals as a hobby, evidence of sensitization to the specific epidermoids involved must be watched for, or these activities should be avoided altogether. The potentially allergic child who easily suffers from respiratory infections should not be encouraged to swim and dive in cold water, and skating should be indulged in very cautiously. Such a child should not mistakenly be subjected to "hardening processes" as cold showers and sleeping in cold rooms. Without competent medical supervision such treatment is more likely to kill than to cure.

Finally the questions arise as to the climate in which the potentially allergic individual is to live and the occupation he is to follow, though the control of these factors is not always practical or expedient. If the family tendency to allergy is expressed by respiratory tract disorders, a warm, dry climate is to be preferred. On the details of this subject there is very little available in allergic literature. Contributions, as the forthcoming publication of Baldwin,17 are greatly to be encouraged. In the choice of a profession the parents of the potentially allergic child and his physician should consider the possible antigens to which he may be exposed and the effect of disabling allergic disease if these occupations are undertaken. A youth highly sensitive to silk should not be encouraged to enter the women's dress goods business; a boy with pollenosis should not become a professional golfer; a boy sensitive to flour dust should not become a baker; or one sensitive to feathers, a raiser of poultry. All these incidents have happened in our practice.

It is realized that the considerations presented in the foregoing discussion are in many instances highly theoretical, controversial, and often impractical. Nevertheless, we believe that the discussion offers a point of departure for the consideration of the life program of the potentially allergic individual. The specialty of allergy is old and accomplished enough so that no apologies need be made for it. On the other hand, it is so immature and its shortcomings so obvious that specific promises cannot be made for the future. We may hope by the application of what knowledge we have concerning the origin of allergic diseases. their natural history, and the healing forces of Nature to make an honest attempt to make life easier for those whose constitutions might well subject them to considerable distress from annoying chronic diseases.

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# STUDIES ON THE MODE OF ACTION AND THE METABOLISM OF VITAMIN D

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UNTIL the present time our knowledge of the mode of action of vitamin D has been extraordinarily meager and may be summed up almost entirely in the observation that vitamin D increases the diminished inorganic phosphate content of the blood in rickets and brings back to normal the diminished calcium content in spasmophilia. As soon as one raises the question how vitamin D brings about the regulation of inorganic phosphates and calcium in the blood, one enters a vast field of speculation.

One of the hypotheses is the assumption that irradiated ergosterol stimulates an endocrine gland. The work of Erdheim, Pappenheimer and Minor.2 Ritter3 and others seemed to indicate the importance of the parathyroid glands in infantile rickets, while the recent publications of Nitschke' emphasized the connection between the lymphoid tissues (spleen, lymph nodes, and thymus) and the thyroid gland in regulating the phosphorus and calcium content of the blood. results of all these studies are, however, far from conclusive, for the simple reason that it has never been possible to isolate any substances other than irradiated sterols that would regulate the inorganic phosphorus content of the blood or would cure rickets. The close relationship between calcium and phosphate metabolism, as well as the discovery by Collip<sup>5</sup> of a hormone regulating calcium metabolism, has, however, made it at least plausible to assume the existence of a hormone regulating phosphorus metabolism.

Two years ago I<sup>6</sup> found that thyroxine elevates the inorganic phosphate content of the blood of healthy infants, an observation that has recently been confirmed by Rietschel. I pointed out, however, that this does not mean that thyroxine can be regarded as the phosphate-increasing substance when rickets is cured by vitamin D. As a matter of fact, I found later that thyroxine does not alter the excretion of phosphorus and calcium through the feces and urine in the same manner as is observed when vitamin D is given.

That is to say, up to the present time we do not know any substance that can be considered a phosphate hormone produced by an endocrine gland through the stimulating effect of irradiated ergosterol.

The importance of this question in understanding the physiologic action of vitamin D and the pathogenesis of rickets, as well, induced me to approach the problem in another way.

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Warkany<sup>9</sup> found that the administration of one large dose of vigantol to rabbits led to a definite increase in the inorganic phosphate content of the blood, an increase which, as I will show later, is not accompanied by a similar effect on the calcium content.

My assumption, in undertaking the studies presented, was that if vitamin D brought about this rise in inorganic phosphate in rabbits' blood by stimulating the production of a phosphate hormone, the chances were that this hypothetical substance might be found in their blood if it was taken at the peak of the vitamin D hyperphosphatemia.

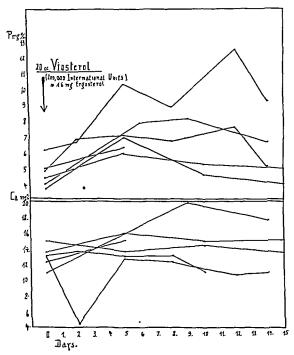


Chart 1.—Curves showing response of inorganic phosphate and calcium in the blood of rabbits after a single dose of 20 c.c. of viosterol in oil (200,000 international units of vitamin D, or about 1.6 mg, of irradiated ergosterol).

The assumption that there was such a substance would be justified if it was found that the blood serum of these rabbits cured rachitic rats by increasing the diminished blood phosphates, provided that it could be proved that the curative substance did not represent irradiated ergosterol itself.

Warkany in his experiments used 100 mg. of irradiated ergosterol given as vigantol. The antirachitic preparations of today, however, are quite different from the vigantol of that time (1929). They contain less ergosterol and certainly fewer toxic by-products. It was necessary, therefore, to repeat Warkany's experiments, using modern ergosterol preparations. These results are now reported.

To rabbits weighing from 3,000 to 4,000 gm. 20 e.e. of viosterol in oil was administered by stomach tube. This is a large dose, representing 200,000 international units of vitamin D; however, it is equivalent to approximately 1.6 mg. of irradiated ergosterol—in other words, a dose less than one-fiftieth of that used by Warkany. The blood of the rabbits was obtained from the femoral vein, and duplicate phosphorus and calcium determinations were made by the titrimetric method of Samson<sup>10</sup> using 1 c.c. of serum for each determination.

Chart 1 shows that, from five to ten days after viosterol was given, the inorganic phosphate content of the blood increased and remained elevated for from the tenth to the fourteenth day, while no regular and definite response was found in the calcium content of the blood.

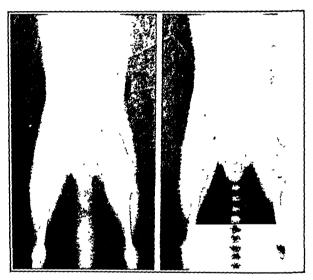


Fig. 1.—Roentgenograms of Rat 5397 (see Table I) before (left) and after ten daily (right) intramuscular injections of 0.6 c.c. of rabbit serum. Rabbit 446, from which the serum was taken, had been given, six days previously, 20 c.c. of viosterol (200,000 international units of vitamin D, or about 1.6 mg. of irradiated ergosterol).

If it were true that this hyperphosphatemic response was due to the production of a phosphate hormone, the shape of the curves in Chart 1 would indicate that its greatest concentration in the blood was on the fifth to the tenth day after the administration of vitamin D, because the greatest stimulation of the phosphate metabolism occurred at that time.

Consequently, I took the blood of the rabbits on the fifth to tenth day after the viosterol had been given and injected daily, for ten consecutive days, 0.6 c.c. of the serum intramuscularly in rats which had been for three weeks on a rickets-producing diet (Steenbock No. 2965).

The results of these five experiments, recorded in Table I, show that the rabbit serum possessed high antirachitic potency in each of the thirteen rats used. The roentgenographic findings in all the rats were without exception the same as those shown in Fig. 1 (Rat 5397).

TABLE I

HEALING OF RACHITIC RATS BY INTRAMUSCULAR INJECTION OF 0.6 C.C. OF SERUM
OBTAINED FROM RABBITS GIVEN 200,000 INTERNATIONAL UNITS OF VITAMIN D
BY MOUTH (20 C.C. OF VIOSTEROL) FIVE TO TEN DAYS PREVIOUSLY

====		X-R	ΛY				=	
j	· ·	HEAL		OF RABBITS   OF RATS'				
RAT	TREATMENT	AFT		OF RABBITS				
NO.		EIGHT	TEN DAYS	P	Ca	Р м <b>с.</b> %	Ca	
		DAYS						
	Rabbit 445 on 11/3/34 received 20	++	+++	6.37	12.4	5.15	18.6	
5393	c.c. of viosterol. On 11/13/34 its	++	+++		}	}	ļ	
5396	blood was taken and 0.6 c.c. of this serum injected daily in the rats.	++	+++					
5397	Rabbit 446 on 10/31/34 received 20	++	+++	10.3	14.6	5.5	14.4	
5399	c.c. of viosterol. On 11/5/34 its	++	+++					
5401	blood was taken and 0.6 c.c. of this serum injected daily in the rats.	++	+++					
5452 5453	Rabbits 447 and 448 on 12/22/34 each received 20 c.c. of viosterol.	++	++++		14.0	5.43	13.6	
5459	On 12/27/34 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.	+++	++++					
5533	Rabbits 458 and 457 on 2/19/35		++++		15.0	3.99	t	
5534	each received 20 c.c. of viosterol. On 2/25/35 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.		+++	-				
5636	Rabbits 468 and 469 on 4/15/35		+++		15.0	4.94	11.2	
5637	each received 20 c.c. of viosterol. On 4/20/35 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.		++++	-				
	Averages			1		5.0	16.9	

<sup>\*</sup>Throughout these studies the rats were killed ten days after treatment had been started so that their blood was obtained for determination of phosphorus and calcium on the same day on which the last roentgenograms were taken. Phosphorus and calcium contents of blood serum are given in milligrams per hundred cubic centimeters, †Serum for determination was lost.

Several control experiments must be reported here before any further discussion can take place.

It was first necessary to prove that rats kept under the same conditions as were the experimental animals did not show any healing without treatment; furthermore, that the serum of rabbits which had never received viosterol did not cure the rachitic condition; and, finally, that the curative effect of the serum of those rabbits which had received the large vitamin dose was not due to the increased phosphate content—a question that could be decided by injecting aqueous solution of Na<sub>2</sub>IIPO<sub>4</sub> in the same concentration as was present in the serum.

The results from the group of control experiments were entirely negative and are presented in Table II.

TABLE II
CONTROL EXPERIMENTS

RAT			HEAL- AFTER	SERUM OF RATS*		
No.	TREATMENT	EIGHT DAYS	TEN DAYS	Р мс. %	Ca MG. %	
538S	None	0	0	3.77	14.0	
5394 5395		0 0	0			
5398 5400 5402	None	0 0 0	0 0 0	5.71	13.0	
5380 5382 5383	Received daily intramuscular injections of 0.6 c.c. of serum from healthy Rabbit 450 which did not receive viosterol.	0 0 0	0 0 0	4.72	13.0	
5385 5389 5391	Received daily intramuscular injections of 0.6 c.c. of serum from healthy Rabbit 44S which had not received viosterol.	0 0 0	0 0 0	4.72	11.8	
544S 5455	Received daily intramuscular injections of 0.6 c.c. of serum from healthy Rabbit 449 which did not receive viosterol.	0 0	0	5.13	10.4	
5649 5618	Received daily intramuscular injections of 0.5 c.c. of serum from infant ill with spasmophilia (whose serum P was 1.7 mg. % and Ca 7.4 mg. %).	0	- 0	4.1	10.2	
5457 5462	Received daily intramuscular injections of 0.6 c.c. of Na, HPO, solution containing 15 mg. % P.	0 0	0 0	2.0	11.6	
	Averages			4.31	12.0	

<sup>\*</sup>See footnote 1, Table I.

Returning to the results of the five experiments recorded in Table I, the conclusion consequently must be drawn that the serums of rabbits which had received, five to ten days previously, approximately 1.6 mg. of irradiated ergosterol (200,000 international units of vitamin D) possessed very high autirachitic potencies. The question naturally arises at once whether or not this was due, partly or entirely, to the presence of vitamin D in the blood. It must, however, be kept in mind that the presence of irradiated ergosterol would not exclude the assumption that there might be a second substance produced by, and present with, vitamin D in the same serum.

The data recorded in Table III clearly answer these questions. Experiments I and II show that the rickets-curing substance can be partly removed from the serum by simple extraction with ether and, furthermore, that it is soluble in oil. Experiments III and IV demonstrate that this substance gradually loses its antirachitic potency if it is overirradiated with ultraviolet light. Finally, Experiments V and VI

show that the ultrafiltrate,\* used in even larger doses than was the original serum, does not contain any rickets-curing substance.

TABLE III

EXPERIMENTS PROVING THAT THERE IS NO RACHITIC HEALING SUBSTANCE OTHER
THAN VITAMIN D IN THE SERUM OF RABBITS GIVEN 200,000 INTERNATIONAL
UNITS OF VITAMIN D BY MOUTH (20 c.c. OF VIOSTEROL)
FIVE TO TEN DAYS PREVIOUSLY

EXPERI- MENT	TREATMENT	RAT	X-R HEAI AFT	LING	SERUM OF RATS†	
		NO.	EIGHT DAYS	TEN DAYS	Р мg. %	Са мс. %
ī	From Rabbits 468 and 469* 15 c.c. of serum was extracted 8 times with 15 c.c. of ether. After evaporation of ether, residue was dissolved in 5 c.c. of wesson oil; 0.2 c.c. of this oil (equal to 0.6 c.c. of original serum) was injected daily intramuscularly in the rats.	5644 5645 5646	+++++++	+++	4.16	11.4
и.	After extraction 8 times with ether, 0.6 c.c. of serum from Rabbits 468 and 469* was daily injected intramuscularly.	5639 5641 5643	+++	+++	3.86	12.0
III	Serum from Rabbits 447 and 448* was irradiated 12 hr. with a Hanau mercury vapor quartz lamp at 46 cm. distance; 0.6 c.c. of this serum was daily injected intramuscularly in the rats.	5449 5450 5451 5461		++ ++ ++ ++	3.88	12.0
IV	Daily intramuscular injections of 0.6 c.c. of serum from Rabbit 458* irradiated for 26 hr, as described in Experiment III.	5544 5536	0 0	0	3.27	11.4
v	Daily intramuscular injections of 0.6 c.c. of ultrafiltrate from serum of Rabbits 447 and 448.*	5454 5458 5460 5463	0 0 0 0	0 0 0 0	2.88	10.8
vi	Daily intramuscular injections of 1 c.c. of ultrafiltrate from serum, of Rabbits 457 and 458.*	5548 5549	0	0	‡	9.8

<sup>\*</sup>The antirachitic potency of the untreated serum is recorded in Table I.

These results prove that the curative potency of this serum was due to a substance that had all the qualities possessed also by irradiated ergosterol: namely, it was soluble in ether and in oil; its antirachitic effectiveness was destructible by overirradiation; and, because of its colloidal state in the lipoid fraction of serum, it was not ultrafiltrable. That overirradiation with ultraviolet light completely destroyed the antirachitic value of the serum makes extremely unlikely the possibility that a second substance was present, as do also the negative

<sup>†</sup>See footnote 1, Table I.

<sup>1</sup>Serum for determination was lost.

<sup>•</sup>Filters were made with an 8 per cent collodion solution in glacial acetic acid. Ultrafiltrates were free from proteins, as shown by the sulphosalicylic acid test.

results obtained with serum ultrafiltrates. The conclusion must therefore be drawn that vitamin D itself produced the healing of the rachitic bone lesion and that, under the conditions described, it does not lead to the production of another substance capable of healing rickets or of increasing the phosphate content of the blood.

Having ascertained that the serum of rabbits to which 200,000 international units of vitamin D had been given contained, five to ten days later, considerable amounts of irradiated ergosterol, I thought it worth while to attempt to learn how long after its administration vitamin D eirculates in vivo in the blood. Such experiments have not, so far as I know, been performed or reported in the literature up to the present time and should reveal the fate of vitamin D within the body in a more physiologic manner than do experiments in vitro.

The same rabbits were used for this group of experiments as for the previous group. Their blood was taken at intervals of one, three, six,

TABLE IV
SHOWING LENGTH OF TIME THAT VITAMIN D IS FOUND IN BLOOD OF RABBITS AFTER ADMINISTRATION OF SINGLE DOSE

							====			
RAB- BIT	DATE 20 C.C. VIOSTEROL	DATE BLOOD	RABBIT SERUM		TIME BE- TWEEN VIOSTEROL	BAT	X-RAY HEALING AFTER		RAT SERUM	
NO. WAS		WAS TAKEN	Р мв. %	Са мв. %	ADMINISTRA- TION AND TAKING OF BLOOD	No.	FIGHT DAYS	TEN DAYS	Р мс. %	Са мg. %
445	12/ 6/34	12/12/34	4.8 4.8	16.2 17.4	1 wk.	5397 5399 5401		+++	5.5	14.4
		12/27/34	6.7	18.6	3 wk.	5446 5447 5456	++	+++	4.9	13.0
		2/23/35	5.1	13.8	11 wk.	5540 5541	0	+	3.9	14.2
448	12,22/34	12/28/34	4.1 7.8	11.0 17.0	1 wk.	5432 5433 5439		+++ +++ +++	5.4	13.6
	,	2/23/35	5.2	15.4	9 wk.	5537 5539	0	+ ?	2.3	13.6
457	2/19/35	2 25 35	4.2 4.3	15.4 16.0	1 wk.	5533 5534	++	+++	4.0	t
	<b>,</b>	3/30/35	1.8	14.2	6 wk.	560S 5609 5610		++	S.5	10.4
		5 3 35			11 wk.	5694 5696 5698		0 0 + ?		

<sup>\*</sup>See footnote I, Table I

tSerum for determination was lost

nine, and eleven weeks following the administration of 200,000 international units of vitamin D (20 c.c. of viosterol in oil, corresponding approximately to 1.6 mg. of irradiated ergosterol), and was tested on rachitic rats in the manner already described.

The experiments summarized in Table IV show that, under the conditions prevailing, the serum of rabbits which had received viosterol was able to establish healing in rachitic rats in ten days, even if the blood was taken as long as from two to two and a half months after the administration of the vitamin. The first distinct decrease in the potency of the serum was noticed after six to nine weeks, and traces could be detected in one instance (Rabbit 445) after eleven weeks. In other words, rabbits weighing from 3,000 to 4,000 gm. needed from two and a half to three months to destroy or excrete 1.6 mg. of irradiated ergosterol (200,000 international units).

#### COMMENT

One finds in the literature no conclusive evidence whatever to support the view that there might exist a hormonal regulation of the phosphate metabolism, as is known to be the case for the calcium content of the blood. The studies presented here, in an attempt to approach the problem in a new way, have proved entirely negative. It must consequently be considered wiser to abandon a hypothesis that cannot be confirmed. It is better, I think, to see in irradiated sterols themselves the only substances the lack of which leads to rachitic hypophosphatemia and the presence of which elevates the inorganic phosphorus in the blood.

In which tissue vitamin D has its point of attack and by which chemical mechanism it increases the diminished inorganic phosphates in the blood of rachitic subjects must still be considered unknown. So far as the low phosphorus rickets in infants is concerned, I found<sup>12</sup> weighty evidence that suggests that the regulation of the intestinal absorption of phosphates does not explain the situation satisfactorily. Further studies on this subject are necessary and are in progress.

The fact that it has now been shown that vitamin D was circulating in the blood for at least two to three months after the administration of a single dose of approximately 1.6 mg. of irradiated ergosterol involves interesting new problems. It is superfluous to emphasize the clinical value of these observations to pediatricians who use vitamin D more or less routinely as an agent for preventing rickets in infants. It is known that damage can be done by overdosage of vitamin D, 12 and it is now shown through these studies that continuous administration may easily lead to an undesirable accumulation because of the apparently low rate of consumption.

The question whether the body destroys or excretes vitamin D cannot yet be decided. The work of Coppens and Metz,14 who reported that vitamin D is destroyed in vitro by blood and lung tissue, makes the assumption likely that it may be destroyed in vivo. The possibility that irradiated ergosterol may also be excreted through bile or through the intestinal wall must, however, be kept in mind. Studies on these problems are in progress.

#### SUMMARY

- 1. The oral administration to rabbits of 20 c.c. of viosterol in oil (200,000 international units of vitamin D, equivalent to approximately 1.6 mg, of irradiated ergosterol) led to an increase in the inorganic phosphorus content of the blood without correspondingly affecting the blood calcium content. This action took place about five days after the viosterol had been given and lasted until the tenth to the fifteenth day.
- 2. In order to learn whether or not this action might be due to the stimulating effect of vitamin D upon an endocrine gland, thus leading to the production of a phosphate hormone, the serum of these rabbits was tested on rachitic rats. The rabbits' blood was obtained five days after the viosterol had been given and was found to cure rachitic rats in from eight to ten days if 0.6 c.c. of the serum was daily injected intramuscularly.
- 3. No evidence was found, however, to justify the assumption that any substance other than irradiated ergosterol was present in this serum or was even partly responsible for its curative potency, because the rickets-curing substance of this serum was soluble in ether and in oil, was destroyed completely by overirradiation with ultraviolet rays, and was found not to be ultrafiltrable.
- 4. When viosterol was given by mouth to rabbits in a single dose corresponding to approximately 1.6 mg, of irradiated ergosterol, detectable amounts of vitamin D were found to be circulating in the blood for from two to three months.

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# DEHYDRATION AND ACIDOSIS WITH CALCIFICATION AT RENAL TUBULES

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THIS communication reports the association of a clinical syndrome and pathologic picture which to our knowledge has not been described heretofore.

The clinical syndrome is characterized by: (1) a persistent dehydration in the absence of excessive diarrhea and vomiting and in the presence of adequate food, salt, and fluid intake; (2) a persistent hyperpnea associated with a sustained elevation of the serum chloride concentration and reduction of the serum bicarbonate content; and (3) deposits of calcium salts within and adjacent to certain renal tubules.

This condition is not simple to recognize as clinical states are frequently seen which appear quite similar until the disturbance of blood electrolytes has been carefully analyzed.

In infants acutely ill with diarrhea and vomiting, abnormal serum concentrations are frequently encountered because of a temporary functional inadequacy of the kidney due to fluid lack. In such cases the abnormal serum concentrations are quickly corrected by the proper administration of water, glucose, and saline. Occasionally chloride acidosis is encountered in dehydrated children coincident to the parenteral administration of physiologic saline. In the cases reported here, the persistent or recurrent hyperpnea and chloride acidosis in the absence of diarrhea, olyguria, and excessive saline therapy and in the presence of an adequate fluid and carbohydrate intake and the continued administration of sodium bicarbonate are strikingly un-Though specific gravity determinations on urine samples and other kidney function tests in these cases were not such as to give conclusive data concerning renal function, the nitrogen retentions and urine examinations for albumin and sediment did not indicate the presence of acute nephritis or inadequate functioning renal tissue. The absence of such pathology was confirmed at necropsy.

Calcification in the renal tubules has been observed in patients with the dehydration, hypochloremia, and alkalosis resulting from upper intestinal obstruction. Cooke suggested that renal changes in these cases were due to the alkalosis. We have seen such a case in a boy with upper intestinal obstruction and mesenteric thrombosis. Necropsy examination showed multiple calcium thrombi in vessels throughout

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the body and a heavy deposition of calcium salts in the renal tubules. Recently, Lightwood<sup>5</sup> has reported a group of six infants with gastroenteritis and vomiting in whom a similar deposition of calcium salts within the renal tubules was found at autopsy. Chemical analyses of the blood in his cases were not such as to give evidence concerning the existence of alkalosis or acidosis.

The picture presented by the four infants described here is striking enough to deserve special mention and characterization. Inasmuch as the dehydration in the infants demanded the parenteral administration of physiologic saline, a procedure which of itself may cause under certain conditions a chloride acidosis, the parenteral fluid therapy is reported in detail in the clinical records given below, so that the unique persistence of the chloride acidosis in these patients can be accurately appraised as a profound metabolic disturbance.

#### CASE REPORTS

Case 1.—E. I.. a baby girl of eleven months, was admitted to the hospital because of repeated vomiting for five months. She was a full-term infant, normally delivered, weighing 93 pounds, who from birth was fed a formula of cow's milk with added sugar. She never gained well and at six months of age weighed but 10 pounds. At that time she began vomiting, and from then until the time of admission she had vomited from one to four times daily. The vomiting was unrelated to food intake and was often projectile. From the age of two months the baby had taken a formula totalling at least 32 ounces of fluid a day and for the previous month had taken at least 40 ounces of formula as well as water which she took in "large amounts." She urinated very frequently and had always been troubled with constipation.

Physical examination showed a small and poorly developed child who was moderately malnourished and dehydrated. She had the appearance of chronic illness and was apathetic, showing little interest in her surroundings and often appearing stuporous. She weighed 12½ pounds. Her temperature was 101° F. The throat was injected, and the tonsils were large and cryptic. There was marked hypotonia of the muscles with hyperflexibility of the joints. There was atrophy especially of the interosscous muscles of the hands and feet. The subcutaneous tissue particularly over the buttocks and thighs was firm and hardened as in sclerema, but the skin was not tense as in the sclerema occasionally seen in dehydrated infants to whom saline has been administered parenterally. The blood showed 85 per cent hemoglobin by Tallqvist test, a red blood cell count of 5,500,000 cells per cubic millimeter, and a white blood count of 20,000 cells per cubic millimeter. The urine was acid and contained no albumin and no cells or casts. The tuberculin and Wassermann tests were negative. Rocntgenograms of the skull and long bones showed nothing remarkable other than an atrophy consistent with disuse.

On admission the signs of dehydration were so definite that the patient was given a hypodermoclysis of 125 c.c. of physiologic saline. She was then placed on a diet of milk, glucose, orange juice, and water. Since the child vomited only once during the first three days and the stools were normal, cereal, egg yoke, and cod liver oil were added to the diet. This diet was fairly well taken. On the fifth day, because of the continued semistuporous condition of the child, a lumbar puncture was done, and a clear fluid under no increased pressure was obtained. The total protein of this spinal fluid was 26 mg. per cent and the chloride 140 milliequivalents

per liter, an elevation of 15 meq. above the normal concentration. This increase in spinal fluid chloride was not remarked until two days later. The result, however, indicates that the blood chlorides were markedly elevated at a time when parenteral saline could not be held as a contributing cause.

During the sixth and seventh days, because of dehydration, the child received a total of 350 c.c. of physiologic saline by clysis and 100 c.c. of 10 per cent glucose by intravenous infusion. On the eighth day, though there had been no diarrhea, and only occasional vomiting, and though the urine output was not scanty (the child having voided six to nine times per day), the respirations became deep and the lethargy increased. The following day examination of the lungs revealed dullness and suppression of breath sounds on the right, and a roentgenogram showed a moderate amount of pulmonary infiltration. A sample of venous blood withdrawn under oil showed a serum bicarbonate content of 6 meq. per liter of serum, chloride of 134 meq. per liter (normal = 103-105), N.P.N. of 95 mg. per cent, and serum protein of 6.4 gm. per cent. The urine was acid and contained no albumin or formed elements. The infant continued to exhibit evidence of dehydration, and there was marked hyperpnea. The condition very rapidly grew worse. As soon as the results of the blood analyses were known, an attempt was made to administer sodium bicarbonate and glucose intravenously. Before this could be completed, respirations ceased.

CASE 2.—C. G., a ten-month-old baby girl, was brought to the hospital because she "had been sickly" and had failed to gain for four months. It was impossible to get a reliable history in any detail even with the aid of an interpreter. The child was born in Italy. She was reported to be healthy and to have nursed well. She was breast fed until eight months of age. Two months before admission the patient was placed on a cow's milk formula. Orange juice and cod liver oil were given in adequate, but not excessive, amounts for one month and then discontinued. The infant's bowels had been regular and stools of normal consistency. There had been no vomiting.

Physical examination showed a poorly developed and undernourished infant of ten months, weighing 11 pounds. The baby appeared small with a long narrow torso, slender extremities and marked frontal bosses. In spite of her weight she did not appear emaciated. The skin was dry, but the baby was not markedly dehydrated. Her temperature was 100° F. Both car drums were full and injected, and there was a mucopurulent postnasal discharge. The lungs and heart were normal, and there was no abnormality in breathing. There was a marked hypotonia of the muscles. The blood pressure was 100 systolic over 60 diastolic. The tuberculin and Wassermann tests were negative. The urine was acid and contained no albumin but showed a few red and white blood cells and granular casts in uncentrifuged specimens. Roentgenograms revealed nothing remarkable other than increased density at the ends of the long bones as seen in retardation of growth.

The child was placed on a formula of whole milk, karo, and water, to yield about 45 calories per pound, and was given orange juice and cod liver oil. Her bowel movements were regular and normal in consistency, and she voided from six to twelve times daily. On the eighth day following admission she had lost six ounces in weight and, though there was no significant elevation in temperature and no vomiting or diarrhea, she gave the appearance of a severely dehydrated child. There was a moderate hyperpnea. At this time a sample of venous blood withdrawn under oil contained 11 meq. of bicarbonate, 121 meq. of chloride, and 138 meq. (normal = 135-140) of sodium per liter of serum. A phenolsulphonephthalein renal test gave 12 per cent excretion in 55 c.c. of urine during a two-hour period. An intravenous infusion of 130 c.c. of 10 per cent glucose plus 2 gm. of sodium bicarbonate and a clysis of 200 c.c. of physiologic saline were given. One quar-

ter of a dram of sodium bicarbonate was given twice daily by mouth. Two days later the venous blood showed an N.P.N. of 30 mg. per cent and a serum sodium and chloride of 141 and 131 meq. per liter, respectively. The child's respirations were rapid, dyspneic, and irregular. The following day signs of pulmonary infiltration developed. The temperature rose to 108° F. before death.

CASE 3.—D. Y., a baby girl, seven weeks old, was admitted to the hospital because of failure to gain throughout life and vomiting during the preceding five days. She was a full-term, 7½-pound baby, normally delivered. She had been breast fed for three weeks and then, because of "influenza" of the mother, had been on a dried milk, and later a condensed milk, formula. Ever since weaning the patient had been constipated and had been given "one teaspoonful of milk of magnesia almost daily." The baby had always acted hungry but seemed to tire easily at feedings and never succeeded in taking much of the formula at a time. When first seen she was malnourished, showed some loss of elasticity of the subcutaneous tissue, was listless, and made only ineffective nursing efforts. No physical abnormalities were found. The urine contained the slightest trace of albumin and rare red and white blood cells. Roentgenograms showed increased density at the metaphyseal margins, indicating retarded growth. There were no calcified areas in the region of the kidneys.

Following admission the infant was placed on a milk, sugar, and water formula and was given orange juice, glucose and physiologic saline between feedings. At the end of three days the child appeared more dehydrated than at entry although she had neither vomited nor had diarrhea. She had voided ten to twelve times per day. Her temperature, which was normal over the first two days, was 101° F. on the third day, and her respirations were rapid. There was a pharyngitis, but there were no signs of pulmonary infiltration by physical or x-ray examination. Because of the dehydration she was given an intravenous infusion of 70 c.c. of 10 per cent glucose and a clysis of 150 c.c. of physiologic saline. During the next two days hyperpnea became apparent, and on the sixth day this evidence of acidosis became marked. The temperature fluctuated between 105° and 98° F. On this day, analyses of venous blood withdrawn under oil showed a marked acidosis due to an abnormally high serum chloride concentration. The serum concentrations determined on this and subsequent days are enumerated in Table I.

The child's course for the next ten weeks was characterized by languor, persistent hyperpnea, and evidence of dehydration, and by an irregular fever with gradually developing signs of pneumonia. Table I indicates the degree of the acidosis, the persistence of the elevated serum chloride concentration, and the serum sodium concentration. The serum N.P.N. was not elevated, and a phenolsulphonephthalein test showed 40 per cent excretion in two hours. Therapy consisted of large amounts of water and sodium bicarbonate by mouth, which the baby took well without vomiting, and repeated intravenous administration of glucose, sodium bicarbonate, and whole blood. The parenteral fluid therapy is detailed in Table I. There was persistent constipution. Feedings of milk, corn syrup, and water giving 50.60 calories per pound, were fairly well taken except terminally. On the twentyfirst day in the hospital the baby had a temperature of 106° F. and a convulsion. Respirations were slow and shallow. The urine was alkaline. The daily 1.5 grams of sodium bicarbonate by mouth were discontinued as it was felt that the sodium administration might have been carried so far as to produce tetany from alkalosis. Unfortunately, serum bicarbonate and calcium concentrations were not determined at this time. However, hyperpnea and chloride acidosis (Table I) were again marked on the twenty-fifth day, and the oral administration of sodium bicarbonate was resumed. On the sixty-seventh day the serum bicarbonate was 11, chloride 123,

sodium 143 meq. per liter and pH 7.10. At this time a urine specimen collected over a period from one hour before to one hour after the collection of the blood sample showed urinary sodium and chloride concentrations, respectively, of 107 and 82 meg, per liter when the rate of urinary excretion was 0.3 per c.c. per minute. Hence it would seem that the urinary excretion was not such as to correct the chloride acidosis effectively. The baby died on the seventy-sixth day after admission.

TABLE I CASE OF D. Y. SERUM CONCENTRATIONS AND PARENTERAL FLUIDS.

DAY	MEQ. PER L.			мс	. PER CE	NT	GM. PER CENT	рн	PAREN- TERAL THERAPY
	HCO <sub>3</sub>	Cl 1	Na	ca	P	N.P.N.	PROTEIN		c.c.
3									70 A*
)		]			Ì	Ì			150 D§
6 8	9	140	148	10	5.5	30		7.05	
8	14	700				1		7.25	i
13	8	130			}	]			į.
16	14 16	$123 \\ 120$			1				
19	10	1	135			33	7.9	7.10	150 Bt
25 26	10	123	100			33	1.5	7.10	70 E
20 32	10	124	140						10 11
35	10	121	140		l				100 E
36			.						90 B
39	9	124	137						90 B
40	1					1			90 B
46	10	128	138						
54	11	123	137				1		
66			· '	1	Ì		1		100 C‡
	1	}	}	1	1	1	1		180 D
67	11	123	143			22		7.10	100 E
68	ŀ	1	!			1			100 C
69	j		j		}				100 C
70	20	1			1				100 C
$\begin{array}{c} 71 \\ 72 \end{array}$	20	94				1			100 C
73		1					-		100 C 100 C
74	18	104	133						100 6
75	10	101	100						70 E
	1ti	of 10 nor	acnt alu		<del></del>	<del>!</del> -	<del>.'</del>	<u>'</u>	1 .0 11

<sup>\*</sup>A, solution of 10 per cent glucose.

As can be seen from Table I there was always a marked lowering of the serum bicarbonate and, except terminally, an elevation of chloride. The serum sodium never reached abnormal heights. Altogether in the seventy-six days of hospitalization some 80 gm. of sodium bicarbonate were given by mouth and 15 gm. intravenously.

CASE 4.-L. H., a two-week-old male infant, was admitted to the hospital because of vomiting and diarrhea. He had been a normal baby during the first week of life. Vomiting, which began the beginning of the second week, was fairly frequent but not definitely projectile. There was a loose but not watery stool passed after each feeding. On admission the outstanding feature of the physical examination was the extreme malnutrition and dehydration. The eyes were sunken, the skin was dry, and there was marked loss of subcutaneous tissue. The mouth was layered with typical thrush. Heart, lungs, and abdomen were normal. pounds compared to his birth weight of 6.5 pounds. The red blood count was

<sup>†</sup>B, solution of 10 per cent glucose containing 1 to 3 per cent sodium bicarbonate. tC, solution of 5 per cent glucose containing 1 to 3 per cent sodium bicarbonate. D, physiologic saline given subcutaneously.

E, citrated whole blood.

5,250,000 per cubic millimeter, the white count 25,000 of which 70 per cent were polymorphonuclear cells, and the hemoglobin was 115 per cent of normal. The urine was acid and contained many cellular casts and crystals, occasional red and white blood cells, and no albumin. The Wassermann and tuberculin tests were negative. Roentgenograms of the chest, extremities, and abdomen showed no abnormality. There was no calcification evident in the kidney region.

Venous blood withdrawn under oil showed on admission a serum chloride concentration above normal, while the serum sodium was below a normal level (Table II). The N.P.N. was markedly elevated. The course of the illness and parenteral therapy are tabulated in Table II.

TABLE II
SERUM CONCENTRATIONS AND FLUID INTAKE. CASE L. H.

}			SERUM	CONC.		FLUIDS				
DAY	MEQ, PER L.			MG. PER CENT		GM. PER CENT	PAREN- TERAL	PER OS		
	HCO2	C1	Na	ca	N.P.N.	PRO- TEIN	c.c.			
1		114	128		150	7.4	60 A			
2					}		100 D	15 on 66 wills - 2 h		
- 2 }							50 E 100 C	1.5 oz. f.f. milk q. 3 h.		
- 1							85 D			
3					1			1.5 oz. f.f. milk q. 3 h.		
4	12	126			31		100 B	2 oz. f.f. m. q. 4 h.; 7 oz.		
							120 D	10% glucose and N. salline ää		
5								2 oz. f.f. m. q. 4 h.; 7 oz.		
								10% glucose and N. sa-		
. }							100 D	line āā		
6							100 B 120 D	2 oz. f.f. m. q. 4 h.; 7 oz.		
							120 1	10% glucose and N. sa- line aa		
7	6	132			48	6.6	200 B	2 oz. f.f. m. q. 4 h.; 15 gr.		
• 1		}	{	1			240 D	NaHCO, in O.J. q. 4 h.		
8	22	124	160	8.0			70 A	2 oz. f.f. m. q. 4 h.; 5 gr.		
			į	}	1		135 D	NaHCO, in O.J. q. 4 h.		
9	1	}	}	l			70 A	2 oz. f.f. m. q. 4 h.; 5 gr.		
			1				135 D	NaHCO, in O.J. q. 4 h.		
10	[			(	(		50 E 600 C	2 oz. f.f. m. q. 4 h.; 5 gr.		
11	}	98	123	6.3	47	4.3	10 Ft	NaIICO <sub>2</sub> in O.J. q. 4 h. 2 oz. f.f. m. q. 4 h.; 5 gr.		
11	}	200	],	0	}	7,.,		NaHCO, in O.J. q. 4 h.		
12							20 E	Breast milk 2 oz. × 4 Skim milk 1.5 × 2		
13	<b>\</b>						615 G;	Breast milk 2 oz. × 4		
1.5							040 (14	Skim milk 1.5 × 2		
11		126	}	10.5	1	5.4		Breast milk 2 oz. × 4		
	1		}		}	-		Skim milk 1.5 × 2		

A. B. C. D. E. solutions as given in Table I.

The essential features of the illness were persistent dehydration and hyperpnea. The day following admission the stools became watery and varied from none to ten per day, but the fluid thus lost never seemed enough to explain the dehydration. The high N.P.N. at entry was evidently due to a diminished kidney function associated with the dehydration since it fell almost to normal on the administration of parenteral fluids. On the eighth day alkaline therapy resulted in elevating the

tF, 10 per cent calcium gluconate.

<sup>1</sup>G, Hartmann's lactate Ringer's solution.

serum sodium to 160 meq. per liter with a resultant increase of the serum bicarbonate to a low normal, but the serum chloride at this time remained elevated. On the eleventh day following 600 c.c. of 5 per cent glucose containing 2 per cent sodium bicarbonate given by continuous intravenous drip over a period of twenty hours the patient had a generalized convulsion. This, in spite of the transfusion giver on the tenth day, evidently was associated with a dilution of the blood by the

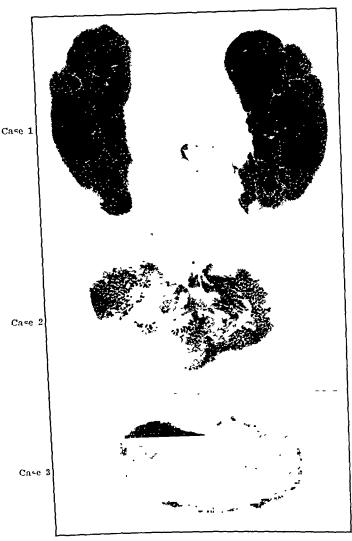


Fig. 1.—Reproductions of rountgenograms of kidneys at autopsy showing the opa

intravenous therapy as indicated by the drop in scrum protein concentration f 6.6 gm. per cent to 4.3 and scrum calcium from 8.0 mg. per cent to 6.3. With dilution the scrum chloride fell to slightly below the normal level, while the ser sodium dropped so far below its normal concentration that the bicarbonate of hardly have been clevated (Table II). Intravenous calcium gluconate, calciuntate by mouth, and a transfusion corrected the low scrum calcium and raised

serum protein concentration. Since the dehydration in the presence of the gastrointestinal disturbance demanded more fluids than seemed advisable by mouth, a continuous clysis of Hartmann's lactate Ringer's solution was started on the thirteenth day. The infant grew weaker and died on the fifteenth day of hospitalization.

#### NECROPSY FINDINGS

The essential pathologic findings in these infants at necropsy were in the lungs and kidneys. An acute terminal pneumonia was present in all four. An otitis media was present in two. Except for a variation in the degree of the calcification the kidneys were strikingly similar and may be characterized as follows:

The kidneys were of approximately normal weight for the age. The capsules stripped with ease revealing smooth, pale surfaces. Sagittal

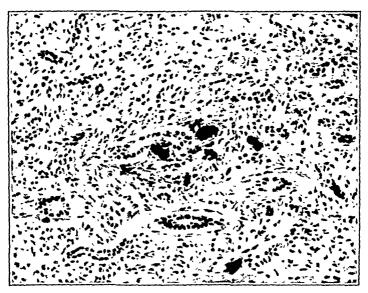


Fig. 2.—The central tubule shows the initial lesion. There are deposits of calcium about the basement membrane but none in the tubular epithelium. Around the tubule there is an increase in fibrous tissue. Several normal tubules are also included. Hematoxylin-cosin stain after Regaud fixation, ×300. Case 2.

section revealed a pale cortex of normal width well demarcated from the medulla. The medulla ranged from pink to gray in color. Throughout the medulla, but particularly at the periphery of the pyramids, small bristlelike deposits barely visible to the naked eye were present.\* These deposits outlined the limits of the pyramids. On passing a knife over these a gritty resistance was encountered. The calices, pelves, and ureters showed nothing remarkable.

X-ray films of the kidneys at necropsy showed a diffuse deposition of calcium salts throughout the medulla (Fig. 1).

<sup>&</sup>quot;In case L. H. no deposits could be noted with the naked eye.

On microscopic examination sections stained by the von Kossa technic gave positive reactions for calcium. The earliest lesions showed calcium deposition within the walls of the collecting tubules between the basement membrane and the epithelial cells and within the connective tissue surrounding the tubules. Frequently the deposits of calcium within the walls of the tubules resulted in an inpouching of the epithelium, a narrowing of the lumen, and degeneration of the epithelial cells. The photomicrographs of Figs. 2 and 3 illustrate these lesions. Many tubules were irregular in shape and contained masses of amorphous calcium in which rings of organic matrix could be recognized. The collecting tubules were most often involved, but deposits of calcium were rarely found in the proximal convoluted tubules.

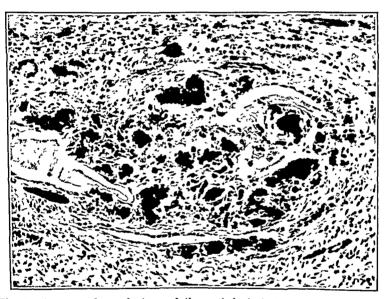


Fig. 3.—A more advanced stage of the pathologic lesion. There are masses of calcium, remnants of tubules, and fibrous tissue in a heterogeneous mass. At the left there is a collecting tubule which is dilated and filled with a hyaline cast. The long tubule near the bottom of the figure presents a calcium deposit beneath the basement membrane similar to that shown in Fig. 1. This indicates the progressive nature of the lesion. Some adjacent tubules are normal though there is an fixation, ×300. Case 2.

Large calcified deposits adjacent to atrophic collecting tubules were often accompanied by foreign body giant cells and surrounded by dense connective tissue derived from the stroma of the kidney, indicative of a process of at least several weeks' duration.

No inflammatory cell infiltration or evidence of nephritis accompanied these lesions. The vascular system throughout the bodies showed no evidence of calcification, nor were areas of calcification encountered elsewhere. The parathyroid glands were normal.

#### COMMENT

Only one of the five patients had definite sclerema. This seems worthy of particular note since the sclerema occasionally seen in dehydrated infants is frequently associated with an elevated serum chloride concentration in the absence of any demonstrable renal pathology.

Hypotonia occurred in a striking degree in two of the four infants. It was not present, however, in a remarkable degree in the two youngest infants who were two and seven weeks of age, respectively. Hypotonia is hard to evaluate and is not usually of diagnostic significance, but in two of these cases it was unusually marked. More commonly a chronically malnourished infant with severe infection is likely to be hypertonic rather than the opposite.

In each of the infants there was evidence of first a respiratory infection and terminally a pneumonia. It is our opinion that these were wholly secondary manifestations such as are seen as terminal events in infants with severe nutritional disturbances of any etiology.

The microscopic picture of the renal lesions indicates that the calcium is first deposited between the tubular epithelium and the basement membrane of the tubule. The smallest deposits were globular, and the deposits never took the form of a layer surrounding tubules or blood vessels in the stroma, even in the largest accumulations.

Calcification frequently occurs in necrotic tissues. In mercury bichloride poisoning, the calcification is secondary to necrosis of the epithelial cells of the tubules, notably those of the convoluted tubules. The calcium salts are deposited first within the necrotic cells themselves, and the early sequences as well as the final picture are entirely different from those of the kidneys under discussion. There was no evidence in any kidney of the infants reported here that calcification was secondary to degeneration of any renal element. It may be pertinent to suggest that the calcium deposits were in locations traversed by calcium salts during normal renal function.

Though an alkalosis from chloride loss due to vomiting may have occurred at some time in these infants, their courses while under observation gave no evidence of a simultaneous alkalosis and dehydration that might have contributed to calcification in the renal tubules. Since no alkali was given one of our patients, the calcification would not seem to have resulted from alkaline therapy.

The absence of any histologic evidence of parathyroid hyperplasia or calcification elsewhere in the body indicates an etiology of the renal calcification other than hyperparathyroidism.

We have observed the association of diffuse calcification at the renal tubules and persistent hyperchloremia and acidosis in two patients\* whose ages, clinical histories, and pathology were different from the cases reported here. Though this association requires fur-

ther study, its occurrence in patients whose pathologic pictures are so different in other respects suggests a relation between the renal lesion and the metabolic disturbance.

A wider recognition of this condition may lead to an understanding of its etiology and a treatment that is more successful than the symptomatic one given our patients

We report a group of four infants and one child who showed a strikingly similar syndrome characterized by persistent dehydration. acidosis with hyperchloremia, and extensive diffuse deposits of calcium salts in and around the renal tubules.

\*M L was a ten-year-old boy admitted to the hospital because of weakness and stunted growth He developed "rickets" at one and a half years of age. At four years he fell and broke his right femur and from that time failed to grow normally Weakness, polydipsia, and polyuria became marked during the preceding two years Examination showed an underdeveloped and moderately emaciated boy who had difficulty in raising himself from the prone to standing position. The urine contained varying amounts of albumin and casts and numerous red and white blood cells. Its specific gravity was limited to 1009. The blood pressure was 110 over 75 Roentgenograms showed general osteoporosis and broad osteoid zones at the ends of the long bones, as seen in rickets tarda or renal rickets, and diffuse calcium deposits in both kidneys. Phenolsulphonephthalein excretion was 70 per cent in two hours. Serum analyses showed normal serum calcium, low inorganic phosphorus, elevated chloride, a low bicarbonate, normal N.P.N. concentrations, and a phosphatase concentration of 10 (normal 03). The low serum phosphorus level and the adequacy of the kidney function were not consistent with renal rickets 1, 1 Roentgenograms showed no cystic areas in the bones. Moreover, masmuch as the urinary excretions of calcium and phosphorus were but slightly above the normal levels, balance data did not support the diagnosis of hyperparathyroidism without a severer kidney insufficiency than seemed present in this case 8 Nephrolithotomy was attempted on one kidney, but the calcification was so diffuse and intimately associated with the renal parenchyma that its removal was impossible without excessive damage to the renal structure. The opaque material removed was shown on analysis to be a calcium phosphate carbonate compound of the composition of bone. During eight weeks the serum chloride varied between 124 and 114 meq per liter and the serum blearbonate never exceeded 16 meq per liter. The patient left the hospital against advice before a diagnosis was made.

advice before a diagnosis was made

The second case was in a patient observed through the kindness of Dr. Fuller
Albright at the Massachusetts General Hospital He was a young man, twenty
years old, who had had hyperparathy rold disease due to an adenoma which had
been removed surgically Diffuse calcification throughout the pyramids of the
kidneys was associated with a hyperchloremia and acidosis

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## Critical Review

### ALLERGIC DISEASES

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CRITICAL reviews, as the term would signify, allow the writer to interpret reports and comment according to his own ideas. It is intended then that the criticisms be stimulating to discussion and further inquiry and in no sense an adequate judgment. The reader may refer to the three preceding annual reviews for the writer's "biased opinion." It is inevitable, with the growth of interest in allergy, that many articles may be overlooked.

A most interesting book by Wodehouse<sup>2</sup> has been published during the past year. It deals with pollen and its significance in hay fever and gives a more extensive discussion of the morphology of pollen grains and the results of pollen surveys than is found in the general texts on allergy. However, much of the discussion in the book is based on early reports which might be considered out of date, and scant attention is given to the pollen problem west of the Mississippi. Gay's<sup>3</sup> impressive volume, Agents of Disease and Host Resistance, includes chapters on Anaphylaxis<sup>4</sup> and Allergy.<sup>5</sup> The latter compiled by David and Beatrice Carrier Seegal are particularly valuable in their discussion of bacterial allergy. Mention should also be made of a German text on allergy by Hugo Kammerer,<sup>6</sup> which escaped attention in last year's review and which the reviewer has not yet been able to examine.

The experimental approach to a study of allergy has received increasing attention. Brunsting and Bailey successfully induced contact dermatitis in guinea pigs. As mentioned previously, the production of primrose dermatitis was successful in Bloch's experiments on human beings. Much of the study of nickel dermatitis has been made on animals, but the induction of contact dermatitis in experimental animals by the use of oil extract is new and perhaps, by some, unexpected. Bernstein combined horse serum with pollens and found that by injection guinea pigs were made susceptible to anaphylactic response from shock injections of pollens. Somewhat similar fortification phenomena have, of course, been observed in other fields.

One of the most important contributions to the theoretical understanding of allergy is the report of the Dutch workers. Benjamin and his associates. These investigators sought an explanation for the fact that removal of the protein from pollen extracts, by filtration or digestion, reduced but did not eliminate the skin-test potency of the filtrate. Choosing the simpler filtration method, they found that when the filtrate was united with substances of large molecular size, but inert themselves, a fortified or intensified skin test was obtained. A

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second filtration left the more active skin-test fraction in the residue. Substances which they tried for this fortification effect on ragweed filtrate were of varied source and type such as human ablumin, aleuronat, casein, gelatin, polysaccharides, and amino acids. The polysaccharides were ineffective, save for glycogen, which is obvoiusly more complex than ordinary polysaccharides. Tapioca, which has been used to "catalyze" the production of diphtheria antitoxin, was a good activator. The amino acids as a group were inert except for leucine, glycine and cystine, which were activators in one instance. They suggested in relation to skin proteins a parallel with enzyme action where there also are noncolloid activators. In general, however, they believe the activation results from the binding or adsorbing of the small "free" groups in the initial filtrate with large (usually protein) molecules, somewhat like the action of protective colloids. If the contention of these workers is correct and the activity of skin testing substances depends on a protection against decomposition in the skin of the small groups by linkage with large molecular substances, an explanation for many of our problems is at hand. will, of course, be further inquiry into the nature of the linkage, adsorption, or binding, and the comparison of the effect of superimposing the small fraction on a site previously used by the activator alone to see if the binding will take place in vivo. While the authors avoid finality in opinion, they present evidence supporting more than localization or dispersion phenomena. It is perhaps mere conjecture, but beyond the skin test study one wonders if in the field of treatment combinations with human albumin warrant trial and whether, as with toxoids, a combination of pollen filtrate with alum would be effective. The ultrafiltered pollen extract is less effective than unfiltered extract in treatment of ragweed hay fever according to the preliminary report of Spain and Sammis.<sup>11</sup> If then the residue with its large molecule linkage is still more effective in treatment, perhaps artificial linkages may improve the natural product. It would also be of interest to know if any part of the immediate passive transfer reactions. such as have been described by Gay12 and others, involves a fortification of the pollen extract as well as a transfer of "reagins."

Osgood and Hubbard, 13 in a less comprehensive report than that of the Dutch workers, found that filtering pollen solutions through a Seitz filter reduced the protein nitrogen and the skin reaction potency of the filtrate. As a measure of the skin excitant they found nitrogen determinations by the trichloracetic acid method better than total nitrogen or phosphotungstic acid precipitation determinations.

Cooke, Stull, Hebald, and Barnard, in their continued study of the relationship of giant and low ragweed, found that extracts of the two ragweeds, when standardized in protein nitrogen content, gave comparable skin tests and constitutional reactions regardless of the source of the pollen. Reactions and constitutional response by passive transfer were greater with the low ragweed so that differentiation might possibly be made with that technic but not by direct test.

Caulfeild, Brown, and Waters<sup>15</sup> have found by passive transfer studies evidence of more than one active substance in the same ragweed pollen. According to their interpretation of the results, there is more than one specific reagin. Caulfeild<sup>16</sup> has also made a preliminary report on the use of pollen carbohydrate as a therapeutic agent for pollen asthma. Interest in specific carbohydrate fractions in bacterio-

logic research has led to therapeutic application. The author found that patients treated with this carbohydrate fraction seemed to require less epinephrine for the relief of attacks than control patients. The author admits the difficulty of comparison of patients and evaluation based on symptomatic response.

Skin testing phenomena have always presented many difficulties in interpretation. Bowman<sup>17</sup> called attention to the necessity of using parallel sites on the arms if comparisons are made in routine tests. This, of course, has been recognized previously and is part of the phenomenon repeatedly emphasized by Alexander.<sup>18</sup> Grow and Herman<sup>19</sup> tested 150 apparently normal individuals, of whom 83 gave positive responses to one or more allergens. The reviewer feels that this proportion would be very good among known allergic individuals. Similar findings have been subject to comment in previous reviews, but they probably deserve emphasis not only because of the delicacy of the test, especially in children, but also because of the lack of parallel with clinical symptoms. The skin test is not an infallible guide.

Hubbard and Osgood<sup>20</sup> determined the protein content of allergen

Hubbard and Osgood<sup>20</sup> determined the protein content of allergen extracts by various methods. The reviewer finds himself in hearty accord with their belief that standardization of the less known allergens is unwarranted. Anderson<sup>21</sup> expresses the rather unorthodox opinion regarding pollen extract preparations, namely, that small doses of pollen mixtures are more efficacious in treatment than concentrated amounts of the chief offending pollens. It is usually customary to give the extracts of pollens according to the indication of the skin test and the most predominant pollens in the local survey. The results have been interpreted as reflecting an increased tolerance from graded injection beyond the usual amount encountered by exposure. Anderson, however, believes that the small mixtures are of value because they resemble the mixtures which the patient inhales. This apparently questions the specificity of selected pollens and does not recognize eareful pollen counts. However, individual variations make didactic statements difficult.

Biederman<sup>22</sup> contends that patients having positive skin tests to pollens present in a season during which they have no clinical symptoms may (in 5 per cent) develop symptoms. Hence, he advocates inclusion of these pollens in hyposensitizing. He believes that patients will show improvement and loss of skin reactions with such a program. The effect of treatment on the skin tests is controversial, and the reviewer can cite several instances where Biederman's conclusions might not be substantiated. As for the results of hay fever treatment, V ander Veer and Clarke<sup>23</sup> find that permanent relief can be expected in 50 per cent of those treated and is most obvious in those having five to eight years of treatment. They feel that successful seasonal treatment favors permanent relief and that the pollen content of the air affects both this and the seasonal relief.

The pollen surveys of Pittsburgh<sup>24</sup> and San Francisco<sup>25</sup> are welcome contributions to this phase of allergy. The old controversy concerning the effect of treatment on the skin test is the subject of a report by Markow and Spain.<sup>26</sup> These authors report, in agreement with Coca.<sup>27</sup> little change after one or two years' perennial treatment. Such variations as were found, they suggest, may be due to loss of potency of the extracts and predicate need of renewal of the extract during the perennial treatment.

The observations reported by Furstenberg and Gay<sup>28</sup> are a greater contribution. The authors noted a purplish cyanosis at the site of the injection of the allergen by obstructing circulation to the skin. The characteristic wheal appeared when the circulation was restored by release of the tourniquet but was less intense than when the circulation had not been obstructed. The tourniquet application apparently made for less dispersion or greater fixation of the reagin with passive transfer. This conclusion was based on the earlier observation of exhaustion of the control site as compared with the experimental site. They hope to show by the use of dyes that perhaps the erythematous flare will involve the dye and differentiate the erythema from the wheal formation. Such observations may shed more light on Lewis 129 theory regarding urticaria.

Dienes and Simon<sup>30</sup> report the flaring up of injection sites in sensitized guinea pigs. Phenomena of this sort have been observed in serum sickness. Further study of Schwartzman's phenomenon will prove valuable in differentiating specific and nonspecific skin responses.

Foshay<sup>31</sup> describes two distinct reactions encountered in testing with antiserums, one a bacteria-specific response, the other dependent on serum sensitization. He used antiserum for tularense and brucella infections. From this observation it would seem less confusing to test for serum sensitivity with horse serum rather than with the antiserum.

Seegal, Khorazo, and Mehlman,<sup>32</sup> by the term "local serum sickness in man," described the effect of repeated intracutaneous injections of 0.1 c.c. of foreign serum. They used sheep, horse, rabbit, and beef as sources and found the serum of the first two more effective in producing the local response in the reinjected site. Purified globulin was less effective than was the unaltered serum. No correlation could be made with the effect of previous parenteral injection elsewhere than at the local site. The question of the slow diffusion from intracutaneous injection and the question of the Forssman antigen effect were raised. There were delayed and hastened reactions and variations in the same individual which suggested multiple rather than single antigens.

A clinical instance of anaphylactic shock was seen by Freedman.<sup>33</sup> The patient, an asthmatic individual, had been given toxin-antitoxin twenty days prior to the fatal injection. Asthma and urticaria had followed the toxin-antitoxin injection. Twenty days later, an intracutaneous test with horse serum used to detect serum sensitivity proved fatal. The reviewer has been told that such episodes are rare, but this occurrence none the less breaks down some of the differentiating features of allergy and anaphylaxis.

The importance of the skin in both allergic and immunologic mechanisms has continued to interest investigators. Kern, Crump, and Cope<sup>34</sup> reported the immunization of allergic and nonallergic individuals by intracutaneous injection of alum-precipitated toxoid. According to them, 0.1 c.c. of this material given intracutaneously is as effective as ten times that amount given subcutaneously. They claimed that unfavorable reactions are less frequent and could well be controlled by tests with the small amounts of toxoid given subcutaneously. This latter method, it will be recalled, was advocated by Thelander<sup>35</sup> for the administration of toxoid to older individuals. The intracutaneous injection would be slower of absorption and the use of a

tourniquet, as advocated by many allergists, could further delay generalized reactions. However, from the standpoint of immunity, despite current acceptance of the Schick test as a guide, such reports might be even more valuable if a check on blood titer were made, as for example by the Kellogg test.

Efron and Silverman<sup>36</sup> obtained positive skin reactions to filtrates of the dysentery bacilli. The skin response was greater to the specific organism of the patient than to other members of the dysentery group of organisms.

Lamb, Anderson, and Nerb<sup>27</sup> claim from their observations of the skin test with filtrates that streptococci are responsible for atrophic arthritis and that they are of value therapeutically. Although different strains of the organism in various foci may be etiologic, the authors recommend autogenous filtrates for which they claim better results than with the vaccine. The significance of positive skin tests to streptococcic filtrates is exceedingly difficult for the reviewer to evaluate. The study of skin tests to streptococcic filtrates made by the Kreuger method has made the reviewer rather skeptical of the interpretation at the present time.

Feinberg and Little38 have undertaken a most difficult but thorough search for the relation of microorganisms to allergy. Testing 600 allergic patients to dry powdered yeasts, they found 65 who gave positive reactions. Reactions to the entire group of yeasts were the rule, and in some instances reactions to fungi were obtained. controls and passive transfer verified the skin test interpretation. Interesting information was given regarding common sources of yeasts, but the authors avoided a didactic clinical interpretation. A second report<sup>35</sup> by these authors dealt with the daily mold spore content of the air. Exposure of Sabouraud's medium on Petri dishes enabled the counting of spore formation for a twenty-four-hour exposure of the plates. A seasonal trend for Alternaria and Hormodendrum was noted, which apparently parallels the clinical symptoms of patients sensitive to molds. The Chicago survey showed greater spore development in the warmer months even though the spores are present throughout the year. A greater pollen count occurred coincidentally with the high spore count. The report stimulates numerous questions as to the rôle of humidity, urban versus rural factors, and air content of inert particles such as soot, etc. Biederman40 reported four patients with allergic manifestations and positive skin tests to yeast. The author advised testing with yeast allergen routinely.

Pennington,<sup>41</sup> in studying trychophytin and monilia in relation to allergy, offers further confirmation of Sulzberger's early reports. The patient reported by Tomlinson<sup>42</sup> had epidermophytosis and gave direct skin tests to six different types of trychophytin extracts. The reactions were without the delayed component described by Sulzberger and Kerr.<sup>43</sup> Tomlinson obtained successful passive transfer but could not demonstrate precipitins (in rabbit experiments). Of the six extracts, the broth culture extract was most potent in polysaccharide and most effective in skin testing.

The nature of house dust allergen, which has been subject to so much controversy, may be somewhat nearer understanding from the investigations of Cohe nand his coworkers.<sup>44</sup> The allergen apparently develops in cotton linters under conditions which exclude the possibility

of contamination with other allergens. Bacterial or mold action is not responsible for the aging process which produces the allergen. Further studies may show the factors in the aging of linters, kapok, and feathers, but at least the development of the allergen for cotton has been rather ingeniously traced. Spain and Newell<sup>45</sup> have reported their use of cellophane as a membrane for ultrafiltration of house dust extract. Many workers are probably familiar with cellophane as a membrane for dialysis.

This year, as compared with past years, has not been marked with efforts to recognize constitutional features of the allergic individual. In a previous review<sup>46</sup> attention was called to the finding of hypochlorhydria in asthma emphasized by the British. An opinion was expressed at that time that perhaps this finding would be shown as secondary rather than causal in its relationship. Such would now be the interpretation of the report by Gillespie.<sup>47</sup> He found hypochlorhydria common under fifteen years of age, perhaps related to excess mucus production and without relation to sensitivity. Disappearance of the hypochlorhydria was noted with clinical improvement. Continuing their studies of the relation of the adrenal gland to allergic phenomena, Cohen and Rudolph48 tried the effect of adrenal stimulation by strychnine. The hypertonicity which resulted quite overshadowed the possible benefit of epinephrine production. The experiment, though of interest academically, is not recommended as being clinically sound. Not adrenal but ovarian dysfunction is suspected by Goldberg 49 as the inciting constitutional factor in his report of climacteric hypersensitiveness to sun and effort. Follicular hormone therapy brought subsidence of the symptoms. It is difficult at the present time to limit the possible inciting or precipitating factors of a constitutional nature. Operations and endocrine upsets are perhaps best considered shock effects. Infections of various types may be similarly responsible as for example the instances of cold urticaria following measles described recently by Kobacker and Parkhurst.50

Matzger<sup>51</sup> has called attention to relief of asthma by administration of intravenous glucose. Wegierko,<sup>52</sup> on the other hand, suggests that induction of hypoglycemia is beneficial. Neither phase of metabolism should be stressed until both are better understood. The reviewer has seen both types of treatment with varying results.

There was a time when without sufficient indication tonsillectomy and antrum irrigations were urged for relief of asthma. Such relief of asthma as was obtained was temporary and was probably the effect of nonspecific shock together with anesthesia. Local anesthesia, particularly that used for antrum irrigations, has long been known to thwart an impending asthmatic attack. Last year mention was made of Coca's report<sup>53</sup> of improvement following surgical measures. And, although anesthesia has been recently advocated by Kahn<sup>54</sup> for semipermanent relief, there has been a swing of sentiment against tonsillectomy in asthmatic patients. The statistics of Kaiser<sup>55</sup> have done much to check the enthusiasm for tonsillectomy, though the reviewer feels that such statistics on mass observations do not necessarily compare with the information gathered from more intimate studies. Bullen<sup>56</sup> has emphasized the aggravation of asthma following tonsillectomy. It is the opinion of the reviewer that surgical procedures may moderate the symptoms of some patients and aggravate the symptoms

of other patients. On such a basis tonsillectomy is neither indicated nor contraindicated by the presence of asthma. Indications depend upon the observation of infection and the appearance of the tonsils. The opponents of tonsillectomy mention the possible "autodesensitization" and filtration by the intact tonsil. Wholesale acceptance of this theory seems to the reviewer a considerable risk to the general health. Although tonsillectomy has been unquestionably overdone, this newer tendency seems extremely reactionary.

The study reported by Ellis<sup>57</sup> concerned erythrocyte sedimentation in allergic disease. He inclines toward the theory that there is an increased suspension stability of the red cells, and the question might be raised as to whether the "spread" of "normal standards" includes instances of minor allergy.

The suggestion made by Cooke and his coworkers<sup>58</sup> that the blood of treated hay fever patients may contain an immune body is of both theoretical and clinical value. Transfusion and intramuscular injection of untreated patients who reacted to the same pollens as the treated donor caused improvement in 16 to 20 patients following transfusion and in 60 to 90 patients following intramuscular injection. This report is in line with the trend of theory separating allergic and immunologic mechanisms (Rich and coworkers). These workers also note a lessening of the passive transfer reaction but with no apparent change in the skin test. The investigators postulate a "blocking mechanism" or substance not to be confused with the reagin. The reviewer wishes they had compared the "nonspecific" effect of blood injected or transfused from nonallergic individuals. Success has been claimed even for autoserous therapy by the Australian physicians, Maddox and Back.<sup>59</sup> A scientific approach, however, was entirely lacking. If Cooke and his coworkers verify their findings, they have made an important contribution. Perhaps combinations of allergen and serum from treated patients will be worth trying.

Mucous membranes have received more attention recently. Walzer, Sherman, and Feldman<sup>60</sup> have developed a modified Prausnitz-Küstner test. After anesthetizing the conjunctiva with 2 per cent butyn, they sensitized the site by subconjunctival injection of serum from individuals sensitive to ragweed and rabbit dander. The reaction to the specific allergens was clear-cut, but exhaustion was usual after the first response. Sensitivity persisted for five tests after an interval of thirty-four days in one case. Otorhinolaryngologists are increasingly interested in allergic phenomena. The review by Hansel<sup>61</sup> is most illuminating. Rowe<sup>62</sup> presented a discussion of nasal and bronchial allergy in childhood. He suggested that many conditions commonly accepted as infectious are on an allergic basis. In accord with the spirit of the times, he emphasizes general measures of nutrition (vitamin, calcium and phosphorus intake) as well as specific measures. He warns against nose and throat surgery as a solution of the asthma problem, though logically allowing it in certain studied cases, despite the report of Bullen previously discussed. The reviewer finds it difficult to believe that the period of September 15 to October 15 is that of the greatest incidence of allergic manifestations. Cohen<sup>63</sup> analyzed a series of 175 cases of nasal allergy and like Rowe found food the most important source of allergens. In contrast with Rowe, he has greater regard for the skin test as a guide for diet restriction. His

dietetic treatment seemed less empirical than that of Rowe. The overshadowing importance of foods might be challenged by those who find considerable incriminating evidence against inhalants. The skin test unquestionably has its failings, as have most of our biologic procedures. It seems unwise, however, to discontinue its use in favor of the elimination diet. Subjective symptoms are not above suspicion in the patient with psychic inclinations, and there is ample evidence which points to the danger of overemphasis of any one test or allergen so far discovered in allergy.

Considerable attention has been paid to iontophoresis or ionization<sup>64, 65</sup> of the nasal mucosa. Alexander's report<sup>65</sup> was preliminary and seemed to show encouragement, there being greater relief of symptoms in patients with negative skin tests. More recent discussion by the Association for the Study of Allergy, and elsewhere, does not seem encouraging. Indeed, evidence was presented which pointed to injury in the nature of fibrosis. Iontophoresis is such an intriguing name, and the popular interest in electric phenomena is so great that the writer marvels that the method had neither origin nor vogue in his state.

Air conditioning has become fairly well established in the armamentarium for respiratory allergy. An interesting paper by Hosmer<sup>66</sup> tells of obtaining relief, sometimes spectacular, in intractible or severe upper respiratory infections. The effects of air conditioning may be particularly beneficial in allergic conditions since it removes the irritant particles and furnishes ideal humidity and temperature. The air-filtering apparatus described by Criep and Green<sup>67</sup> is a far cry from the elaborate one of van Leeuwen.<sup>68</sup> Their apparatus has no effect on temperature and humidity but does remove pollen and dust particles efficiently. Symptomatic relief while in the air-filtered room was obtained in 61 patients with hay fever and asthma. The simplicity and the moderate cost of the machine are most commendable.

The past year has brought several reports dealing with pathology. This phase has seemed to be neglected because, except for the important experimental work, routine pathology has offered little explanation for functional disturbances. Kline and Young, 69 following Rossle's<sup>70</sup> theories, offer a discussion of reversible and irreversible allergic reactions. While adding to the confusion of nomenclature by the use of terms such as "hypergy," "hypo-ergy," "anergy," and "normergy," they have nevertheless endeavored to clarify the varying types of response. Fried,<sup>71</sup> working with rabbits, was able to produce an exudative inflammation of the lungs resembling lobar pneumonia. The rabbits were sensitized to horse serum and the shock injection was given intratracheally. Miller 2 and his associates report what may be the clinical parallel, "allergic bronchopneumonia." One is reminded of the splenic pneumonia or perifocal infiltration seen in tuberculosis. However, in the instance of pneumonia and respiratory infection seen in allergic children, the thesis is not as yet without controversy. The rôle of mucous plugs in atelectasis might explain some instances quite apart from allergy. Wilmer, Eiman and Miller73 report the necropsy of a patient with essential bronchial asthma. Roentgen findings, antemortem and postmortem, are compared. The patient had had pollen asthma in his youth and a great emotional strain in adult life, which definitely accentuated his asthma. The presence of a renal stone had

prompted parathyroid investigation. Clinically, the patient presented a picture of profound emphysema in his terminal illness. The case illustrates the confusion in trying to recognize pathology related to functional disorders in the adult who has had superimposed and perhaps unrelated disease.

Michael and Rowe<sup>74</sup> report two postmortem studies of adults with chronic asthma. There was found in the lung smooth muscle hypertrophy, swelling of the mucosa (as was found in Wilmer's patient), mucus in the lumen, thickening and hyaline degeneration of the basement membrane and myositis of the bronchial muscle. One of their patients had an enlarged thymus and a small aorta and heart. Waldbott. 75 continuing his theme of anaphylactic rather than thymic death in infants, reports autopsies on two infants with acute asthma. Most of the findings of Michael and Rowe were absent, the main lesion being pulmonary edema probably from capillary permeability and secondary right ventricular dilatation. He emphasizes that these findings have been reported in the instances of "thymic death." The lymph gland enlargement suggests that perhaps some of the instances of mesenteric adenitis first described by Brennemann<sup>76</sup> may represent the pathology of allergy sensitivity. Some of the cases of mesenteric adenitis proved by exploratory laparotomy, which the reviewer has observed, have been in children with known food intolerance.

The literature of the past year contains many reports dealing with The pediatric department of the University of Minnesota has been studying blood fats in relation to various diseases. Hansen<sup>77</sup> contends, with regard to eczema, that there is a lowered amount of unsaturated fatty acids in the serum which may be raised by oral administration of unsaturated fat such as purified linseed oil. bleet and Pace, 78 in a clinical application, reported improvement in a group of 87 patients treated with maize oil. They offered no chemical determinations to support the rationale of their treatment. Faber and Roberts,79 in a small series of 15 eczematous infants and 16 controls, found that although the fatty acids tended to be low in the serum of eczematous infants, the difference was not sufficient to warrant Hansen's contention. They were not able to confirm the beneficial effects of corn oil. Taub and Zakon80 are more devastating in their comments. They were unable to confirm Hansen's findings, and they called attention to the danger of indiscriminate use of linseed oil which may serve as the vehicle for cottonseed allergen. It would appear that the rôle of the unsaturated fatty acids (like hypochlorhydria previously discussed) is secondary and that sufficient studies to warrant a statistical analysis do not justify the interpretations given by some workers.

The use of soybean milk for feeding 205 infants was reported by Rittinger, Dembo, and Torrey. They made careful observations on weight, growth, blood studies, and x-ray studies and found this vegetable milk an adequate food. The reviewer is forced to change his earlier view that this protein of vegetable origin is not a satisfactory "tissue builder." However, the inference which they make with regard to its use in eczema, based on the high ratio of unsaturated fatty acids, seems unwarranted in view of other reports. The cereal mixture of Tisdall. Drake, and Brown<sup>\$2\$</sup> was studied by Blatt and Schapiro. Their observation of no allergic manifestation is of inter-

est, but without more data regarding the possible allergic susceptibility in the group the statement is of little value.

Hopkins and Kesten<sup>84</sup> report their observations and ideas on a group of 75 patients varying from one to twenty-seven years of age. The importance of family history and the rôles of certain foods are stressed. Silk and wool are considered inhalant ingestants rather than contact excitants. They reviewed much that is already familiar. Cobb<sup>85</sup> has published menus for the elimination of the common food offenders in childhood allergy. These are quite useful.

Hill and Sulzbergersc present what might be called an orthodox American theory regarding the "evolution of atopic dermatitis." Infantile eczema and neurodermatitis in childhood and adult life are considered part of the same general mechanism. Admitting the hereditary background in about half the cases, they acknowledge placental transmission and acquisition of hypersensitivity. There was no discussion of the factors which might explain the frequency with which skin manifestations are limited to infancy in some and persist throughout life in others. Schiff, in discussing neurodermatitis of childhood, gives a much more empirical program for treatment than that which the allergic theory indicates. Advising such foods as radishes and cucumbers in the raw fruit and vegetable diet for three-year-olds is rather surprising.

Ratner<sup>88</sup> has reiterated his thesis of acquisition and placental transmission. In a general discussion of milk allergy, he advises the use of heat to alter the lactalbumin and globulin fractions which are the chief offending fractions. This author<sup>89</sup> has also reported in more detail the results of animal experiments which show that the (noncasein) whey fraction loses some antigenicity on evaporating or heating. Concerning the sugars used for infant feeding, his experiments showed that malt extracts were often offenders because of the barley but that corn syrup and pure dextrimaltose were free from allergic implication. Tallerman, ousing the passive transfer technic of Prausnitz-Küstner, found evidence of circulating reagin in the blood of infants with gastroenteritis. He suggests that clinical toxemia may be related to an allergic reaction. This was precisely the thesis of the work of Schloss and Anderson several years ago. Walzer and Walzer, also using the passive transfer method, obtained positive reactions after oral administration of the antigen. This, of course, is further evidence of the absorption of unaltered proteins.

The views of Worringer<sup>93</sup> on the problem of eczema are more acceptable than those of Schiff.<sup>94</sup> Worringer is primarily interested in eczema and allergy of infants and has discussed various theories of origin, postnatal acquisition, intrauterine or placental transmission, and hereditary factors. The same views are again expressed in his observations regarding infantile eczema.<sup>95</sup> He rejects the theory of passive transfer in utero and feels that Ratner's placental transmission does not represent the usual mode of sensitization. He strongly supports the hereditary factor inherent in both male or female germ cells and supports his contentions with convincing reasoning. The reviewer is in agreement with his refutation of sensitization through maternal milk.

maternal mink.

The acquisition of sensitivity (or induction of latent capacity) is attracting considerable attention. Goldman and Pfosi<sup>96</sup> studied lacquer

dermatitis. The authors tested 61 patients by a patch test suggested to determine the extent of similarity between natural lacquer (Japanese) and Rhus toxicodendron. There were 29 positives to the natural lacquer, two to the artificial lacquer. There were 12 positive reactors in the control group of 98, which included six individuals with "neurodermatitis." No specific note is given regarding the response in the patients with neurodermatitis, nor is there any discussion of the effect of age. The group included patients as young as two years, at which age the skin is notoriously susceptible to nonspecific irritation, a fact which makes the patch test of doubtful interpretation. The authors stress the rôle of industrial exposure.

Colmes, Guild, and Rackemann,<sup>07</sup> in studying the influence of occupation on sensitization, reported a rather high percentage of positive wheat tests in thirty-two bakers. Only one verified instance of clinical sensitivity could be found, but the authors emphasized acquisition rather than hereditary predisposition as etiologic. Duke's report<sup>98</sup> on wheat millers' asthma, with a study of the morphology of the wheat germ, suggests that an inhalant from the "bearded" portion of the outer cells may be responsible. He found that wheat dust extracts gave positive reactions where the ordinary fractions failed. Passive transfer verified the presence of reagins for the wheat hair factor as did also the microscopic study of dust collected in a fashion similar to that used in pollen surveys. Comparison with tests of house dust extract was not offered.

The report of Vaughan and Fowlkes<sup>99</sup> on allergic reactions associated with cohabitation might be mentioned in reference to acquisition and the effect of exposure though it is not occupational. Details may be omitted since it is the writer's experience with his medical students that this is one report which will not be overlooked. The same may be said of Cooper's<sup>100</sup> report on semen allergy in children. Both reports are unusual but authentic.

Hypersensitiveness to insulin was studied by Sammis.<sup>101</sup> Reagins were found for both animal and synthetic insulin. The previous discussion of Tuft<sup>102</sup> is perhaps more comprehensive. The report last year

by Bayer<sup>103</sup> on desensitization in insulin allergy is of value.

Jiminez-Diaz and Cuenca<sup>101</sup> report instances of unusual antigens responsible for asthma. Linseed insect protein, chicory, and tobacco are mentioned by these Spanish investigators. Chobot<sup>105</sup> discusses the significance of skin tests to tobacco in allergic children. He tested 52 patients; 6 gave marked reactions, 2 moderate, and 11 mild reactions. The reviewer has found that interpretation of the tobacco reaction in young children is very difficult. Babcock's report<sup>106</sup> on catgut allergy suggests an interpretation of some of the peculiar reactions in sutures heretofore enigmatic. No evidence was found by Stevens<sup>107</sup> incriminating cottonseed allergy from gin.

Cutaneous allergy following amidopyrine ingestion was reported by Taussig. OS Skin tests were negative, but the clinical response of angioneurotic edema was definite. There had been an interval of time between the first ingestion of the drug and that which precipitated this response in the patient who was known to be allergic. New also in the lore of potential allergens is the suggestion of Fonde and Fonde. They suspect the "honeydew" of the live oak trees of the South as a cause of hay fever. The material is the product of small

insects infecting the oak leaves.

Blumstein<sup>110</sup> found 19 positive skin reactors to buckwheat in a group of reactors, mostly from inhalation (bakers). He found no evidence to incriminate buckwheat in relation to photosensitization.

At the University of Michigan, Sheldon and Randolph<sup>111</sup> found 127 of the student patients with migraine. There was a family history of allergy in 81.6 per cent of this group, mostly from the maternal side. An elimination diet was effective in about 38 per cent of the cases. Vaughan<sup>112</sup> is also of the opinion that food sensitivity is a factor in migraine. He found about 70 per cent of the instances of migraine associated with allergy in the absence of organic conditions, though it is not clear how completely these organic conditions are ruled out. Supervision, cooperation, the use of skin tests, food diary, and the leucopenic index are responsible for his rather high percentage of success. The reviewer still feels that migraine is pretty much of a riddle and that many other conditions besides allergy must be considered.

Psoriasis is the most recent disease to be suspected as an allergic manifestation. Adamson<sup>113</sup> tested the skin and injected the extract of psoriatic scales. The latter procedure is suggestive of a possible conspecific effect as in autoserous therapy. The conditions in the newborn which Mayerhofer<sup>114</sup> considers allergic are toxic erythema, rylorospasm, melena, and hydrocele. The reviewer is most skeptical but admits the report should stimulate investigations in this newer field.

On the subject of therapeutics, the readers may find the Cook County Hospital Therapeutics of value. While dealing chiefly with contact dermatitis, the authors, Fantus and Cornbleet, 115 apply accepted allergic methods for diagnosis and treatment. Thiberge 116 compared the effects of histamine and typhoid protein in control of asthma and hay fever. He found both useful as nonspecific agents but felt typhoid split protein safer. The new vaporizer 117 for epinephrine inhalation has proved of definite value in the treatment of severe asthmatic attacks. Dzsinich 118 treated 15 asthmatic patients with graded histamine injections. He feels that the use of this agent is justified even though he did have some failures. The reviewer would call attention to the fact that the present enthusiasm for histamine probably dates from Lewis 119 study of urticaria. Yet Lewis was most careful to use the term histamine-like in reference to the toxin from cell injury. The drug is not without danger even in minute amounts and should not be advocated for indiscriminate use.

The study of allergy is still in its infancy. While empirical treatment should have a trial, it is not a substitute for detailed sleuthing and study of individual patients. This naturally makes it difficult to accumulate careful studies of sufficient magnitude to warrant statistical analysis.

The Association for the Study of Allergy has started a program of certification for clinics dealing with the allergic problem. The reviewer has mixed feelings about such standardizations. Starting with the American Medical Association and the College of Surgeons, there has been a rush to specialty organizations and programs for certification. In a subject as new as allergy is there not still room for non-conformity? Is there not danger in setting standards for technic that are controversial or in cramping initiative and individual observations? Perhaps it will be found a difficult but "noble experiment."

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#### American Academy of Pediatrics

#### **Proceedings**

## FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

New York City, June 7, 1935

#### Round Table Discussion on Encephalitis

Chairman: Dr. Josephine B. Neal, New York, N. Y. Assistant: Dr. Thomas M. Rivers, New York, N. Y.

The meeting was called to order at 2:30 P.M., at the Hotel Waldorf-Astoria, by the chairman, Dr. Josephine B. Neal.

CHAIRMAN NEAL.—As the years have passed since encephalitis has been more or less prevalent, the new problems that have arisen have far outstripped any advances that have been made in the solution of them.

It, of course, is quite impossible to cover the subject of encephalitis at all adequately in a short discussion. There is one point that I would like to emphasize—however, we so often hear the term "von Economo's encephalitis" as if this were a separate and distinct entity that should be recognized clinically. People who use this expression are, I think, quite unfamiliar with what von Economo himself wrote. In describing the small group of cases that he studied and worked up so admirably in Vienna, he took occasion to emphasize the wide variation in the clinical symptoms, and he stated that the only one consistent finding was the lesions in the basal ganglia.

In my part of the discussion I shall not go into the pathology of encephalitis, but I remember hearing Dr. Tilney say that the reason lesions in the basal ganglia were so much emphasized was mainly that pathologists had not searched sufficiently in other parts of the brain, that in encephalitis the lesions were, as a matter of fact, widespread.

Another point worth considering at this meeting particularly is that encephalitis occurs more frequently in children than is generally known. Encephalitis attacks all ages, from children only a few days old to adults in the seventies and eighties. The acute stage of encephalitis very often passes undiagnosed.

The clinical picture in children is very widely varied, and in these later years since encephalitis has been prevalent, we have seen a relatively large number of cases of encephalitis following measles, chickenpox, whooping cough, occasionally scarlet fever. The meningoencephalitis following mumps has always been more or less prevalent, even before epidemic encephalitis became prevalent. This seems to be a rather clear-cut clinical picture of meningoencephalitis, and it may precede the development of the parotitis.

In these other forms of encephalitis, including that following vaccination, of which fortunately we have had very little in this country, the clinical picture varies very greatly, and these patients also in certain instances go on to the chronic stage of

the disease, in which they show varied manifestations. When encephalitis first became prevalent, we thought that the chronic stage was a sequela of the acute stage, and, if it were to develop at all, we expected it to develop within a matter of months or at the most a year. As time has gone on, however, we find that patients may be restored apparently to complete health and may remain so up to ten or more before the chronic stage develops. Of course, in the majority of cases it does make its appearance within the first five years

Encephalitis is the most terrible disease that I know, and its effects in children are even more devastating than in adults. In children encephalitis in any form is frequently followed by mental deterioration and moral degeneration, with or without definite neurologic changes. Of course, a certain number of them may go on into the parkinsonian stage at a later date, and we do see parkinsonism developing occasionally in fairly young children, but on the whole the mental and moral changes are much more pronounced than the actual physical changes. In adults, on the other hand, there are rarely changes in the mentality or in morals.

The question of encephalitis has been still further thrown into confusion by the development of the St. Louis epidemic. Up to that time, many of us had hoped that a single etiologic agent might be responsible for these cases. The etiology of encephalitis following vaccination, measles, and other acute infections was an entirely open question. But with the development of the St. Louis epidemic and the isolation of a new virus, we now recognize the fact that there must be more than one etiologic agent. How many etiologic agents there are time alone can tell

As time has gone on, the clinical picture of encephalitis has perhaps changed more or less, that is, the preponderance of the symptoms have changed, and whether this is due to coming in of the new viruses or to other factors, I do not know. Dr. Rivers can answer that much more adequately.

The diagnosis of encephalitis must be made by ruling out as many diseases as possible. Of course, meningitis, particularly tuberculous meningitis, may be ruled out by lumbar puncture. A Wassermann test must be made on all spinal fluids in cases of suspected encephalitis. In encephalitis there is ordinarily a change in the spinal fluid, an increase in cells, which varies very greatly, usually a preponder ance of mononuclears, occasionally polymorphonuclears, often an increase in protein and a normal or high spinal fluid sugar content. There may be an increase in cells without much change in the protein, or the increase in the protein may be much greater than the relative increase in number of cells. Occasionally we see cases, undoubtedly encephalitis, in which the spinal fluid findings are within normal limits.

If patients suffering from encephalitis have increased pressure of the spinal fluid, lumbar punctures should be performed as indicated until the pressure be comes normal. The intravenous injection of hypertonic glucose aids in reducing the increased intracranial pressure. Hypertonic glucose also serves as a cardiac stimulant and is of general benefit to the patient.

On the premise that a virus closely allied to the herpes virus may be the cause of certain forms of encephalitis, we have been using a vaccine in treating cases both in the acute and in the chronic stages. A certain percentage of the patients treated in the chronic stage have shown some improvement over a period of years. Whether improvement is due to the vaccine or not, I have no firm conviction. We have treated a fairly large number of patients in the acute stage with the hope that the development of the chronic stage might be averted. So far, and this is up to a period of five years, none of the patients treated in the acute stage has gone into the chronic stage of the disease

It is only by following these cases over many more years that we can be sure whether or not the vaccine was of any value in building up a sufficient immunity to avert development of the chronic stage.

One could talk about encephalitis indefinitely. At this point I will ask Dr. Rivers to go on with the discussion.

DR. THOMAS M. RIVERS (New York).—Encephalitis means nothing more than an inflammation of the brain, and it can be caused in a number of ways, for instance, by protozoan parasites as in African sleeping sickness or as in toxoplasma infections of rodents, by fungi, by bacteria as in encephalitis complicating bacterial endocarditis, by spirochetes as in paresis, or by rickettsia as in typhus fever. In addition to these infectious agents which produce an inflammation of the brain, there is another group of agents known as the viruses or filtrable viruses which produce encephalitis; and, more or less by consent, when one says encephalitis, one usually thinks of inflammation of the brain caused by the viruses. That is what I am going to talk about this afternoon. That is what Dr. Neal has been talking about already.

Encephalitis is certainly not a clinical entity. Some day we will be able to divide the large group of cases of encephalitis into smaller groups and assign to each one its real etiologic agent. Until we can do that, the whole field of encephalitis is going to be in a very much confused state.

Our attention was first called to encephalitis forcibly during and after the war by the so-called von Economo's encephalitis or lethargic encephalitis or epidemic encephalitis. All of those names are very unfortunate because any encephalitis occurring epidemically can be epidemic encephalitis; lethargic encephalitis, von Economo's disease, may be anything but lethargic because the patient may be highly agitated. Thus the names that we have used to designate the cases of encephalitis occurring during and after the war, that is von Economo's lethargic encephalitis and epidemic encephalitis, are certainly inadequate and confusing.

We will discuss that group of cases first. I will hazard the statement that the majority of the cases occurring pandemically were caused by a single etiologic agent even though they were very different clinically. As to whether any individual case that was seen at that time represented epidemic encephalitis, I don't think it would be possible for one to say. As to the etiology of this group of cases, we are still ignorant. Of course, a number of people contend that herpes virus, the virus which causes fever blisters, is responsible. Levaditi in France, is particularly in favor of such an idea. Dr. Gay and others in this country favor it also. Personally, I am rather opposed to the idea, and I agree with Dr. Neal, who has just said that the etiology is decidedly still an open question.

Now we come to another group of cases, those that occurred in St. Louis in 1933. As a whole, that group of cases was clinically different from the major portion of the cases which occurred during and after the war. In the first place, practically all of the patients went back to work within three weeks. In another respect, the cases in St. Louis were different from the ones that occurred after the war: the age incidence was distinctly higher in the St. Louis group than in the other type. Furthermore, a number of people were able to recover a virus from the cases in St. Louis. As a matter of fact, it was rather easy to recover a virus from those cases. The virus can be transmitted to monkeys fairly well and very well to mice. If the cases that occurred after the war had had a virus similar to the one in St. Louis, I am sure that a large number of people would have recovered it, because excellent men attempted to transmit the disease to lower animals without success. Thus, the cause of the St. Louis encephalitis is definitely known. It is a very small virus, one of the smallest. Its diameter is about 15 to 20 m $\mu$ . It won't multiply on ordinary media and can be carried only in some susceptible host.

Serum from the majority of the individuals who have recovered from the St. Louis type of encephalitis neutralizes the virus that has been isolated. On the other hand, serum from individuals who had von Economo's or pandemic, epidemic, or lethargic encephalitis will not neutralize the St. Louis virus.

Thus we have a certain amount of clinical evidence that the so called von Economo's disease and the St. Louis disease are different, but we have excellent experimental evidence to show that they are different.

Not only did the patients who recovered from the St. Louis type of encephalitis have neutralizing serums for this virus but serums from many of the contacts in the St. Louis area who did not have any visible disease also possessed neutralizing properties, whereas serums from normal people in France or normal people here in New York City do not neutralize the virus.

Another question arises as to whether the St. Louis type of encephalitis has occurred anywhere else in the world, or whether it occurred before 1933. Yes it occurred in Paris, Ill, in 1932. Dr. Webster has been able to get serums from individuals who recovered from a small epidemic of encephalitis in Paris, Ill., and he has found that all of them neutralize the St. Louis virus. In 1933, we had two cases of the St. Louis encephalitis here in New York. Not only did the St. Louis virus occur in this country before 1933, but it has occurred since, as Di. Webster is now able to show that a certain number of cases occurred in various places during the summer of 1934.

So it looks as though we may have a definite encephalitis caused by a virus that we can isolate and recognize serologically. Now, is there an encephalitis like the St. Louis encephalitis occurring anywhere else in the world except in the United States? There is in Japan, a type of encephalitis called summer encephalitis. It occurs mostly in old people or in people beyond middle life. It occurs in the summertime and has a high mortality. Epidemologically, clinically, and pathologically the summer encephalitis in Japan looks very much like the summer encephalitis in St. Louis in 1933, but serums from the people who have recovered from the summer encephalitis in Japan do not neutralize the virus which caused the epidemic in St. Louis.

The disease in St Louis and the disease in Japan are alike clinically, epidemo logically, and pathologically; yet they are caused by viruses which are not serologically similar. That may seem very peculiar, but it is not very peculiar when one considers encephalitis in lower animals. For instance, we have here in the United States equine encephalomyelitis. It attacks horses both in the western and in the eastern part of the continent. The virus which causes the disease in the East—the disease is very much alike in the two localities—is different from the virus which causes the disease in the West, that is, they are different immunologically. So it is not peculiar that we have in St Louis an encephalitis like that in Japan and still have them caused by viruses that are immunologically different.

Now we come to the encephalitis which follows measles, chickenpox, vaccination against smallpox, vaccination against rabies, etc. Clinically it is like any other encephalitis. It has bizarre manifestations in the individual case, such that in the individual case it is almost impossible to be sure of what one is dealing with except that it is postinfection encephalitis

Such cases for the most part are different pathologically from the types of encephalitis that I have already mentioned. In the majority of cases of post measles, postvaccinal, postvaricella, postrabic vaccination encephalitis, perivascular demyelination occurs. That does not mean that every patient who has encephalitis following measles is going to have perivascular demyelination because a certain number of such patients have died and at autopsy have failed to show perivascular demyelination. The group of cases of encephalitis showing perivascular demyelination is distinctly different from the other cases of encephalitis that Dr. Neal and I have been talking about

A number of people have suggested that the vaccine virus or rabic or varicella virus is responsible for this land of encephalitis. My own opinion is this: No known virus acting directly on the central nervous system produces a perivascular

demyelinating type of encephalitis. Therefore, it would be very unlikely for the viruses of measles, rabies or vaccinia to produce a perivascular demyelination as the result of their direct action upon nerve tissue. I do not know whether you get that or not: I think it is a very important fact. Vaccine virus put into the brain of a large number of animals produces encephalitis or meningitis, but it does not produce a perivascular demyelination. Rabic virus put into the brain of an animal never produces perivascular demyelination. Let the encephalitis which follows vaccination against smallpox and encephalitis which follows vaccination against rabies is characterized in most instances by a penyascular demyelination. Now, it would be a very peculiar virus that would attack the myelin and not attack the cells If our conception of viruses is correct, that is, if they are intracellular paiasites, then the neurons, the nerve cells, should be damaged, but in the typical postvaccinal cases, there is little or no damage of the nerve cells The main picture is a loss of myelin So, without knowing what causes the demyelinating encephalitis follow ing mersles, vaccination, etc, I am postulating that it is very unlikely to be a virus.

Is there any evidence in regard to the mechanism of demyelination in these cases? A number of people think that the permascular demyelination that follows vaccina tion against rabies is due to the biain substance injected during the process of vaccination. A certain amount of experimentation has been done. If one repeatedly injects sheep brain into rabbits, about 30 per cent of the animals become paialyzed Unfortunately, no pathologic changes in the central nervous system have been found to account for this paralysis. We had an idea that maybe demyelination is not possible in the rabbit. The rabbit would become paralyzed, but demyelination could not be produced. We transferred our work to the monkey. We have been repeatedly injecting monkeys with normal rabbit brain, and for two years in succession we have been able to paralyze monkeys. With repeated intramuscular injections of normal rabbit briin, we piralyzed two of eight monkeys the first year and seven of eight monkeys the second year. When we killed the monkeys and examined them, we found perivascular demyclination. Unfortunately, the picture is not identical with that seen in the human being There are a number of things in the monkeys so different from what we see in human beings that I don't know whether we have solved the question of perivascular demyelination or not. I am inclined to think we have not, but we do know that we can paralyze monkeys and get permascular demyelina tion by repeatedly injecting into them normal rabbit brain

We have not been able to transmit this demyelinating disease to other monkeys in series. We cannot transmit it to rabbits, guinea pigs, or mice. We believe, nevertheless, that it is a result of the repeated injections of normal brain

I think for the time being that the etiology of the perivascular demyelinating type of encephalitis that following various infectious diseases has to be considered an open question. I do have very strong convictions, though, that it is probably not caused by the direct action of a virus

The meningoencephalitis of mumps is probably caused by the virus of mumps. I do not think that we need to go any further into that question. The experimental proof has not been brought yet that that is the case, but I think that it will be brought now that Dr. Goodpasture has been able to transmit mumps to monkeys.

We have talked in a general way about a large group of cases in St. Louis and about a large group of cases which occurred during and after the war, and about a large group of cases which occurs after certain acute infections. What we have said in regard to these groups as a whole is probably true, but I am quite convinced that there are many other smaller groups of cases of encephalitis the etiologic agents of which have not been found which are being classified either with the St. Louis group or with you Economo's or epidemic group. I think the best proof I can give you of this is that just recently we have been able to isolate a new virus from two

human beings with involvement of the central nervous system. Two adults came under our observation almost simultaneously, one in Princeton and one in New York. The clinical picture in these two cases was almost identical. The individuals were sick with something that looked like influenza for a few days and then went back to work feeling bad. Then after they had been back at work for a few days, they were taken ill with terrific headaches. The headaches were so bad the patients could not sleep and various drugs gave no relief. One of the patients was seen by a physician here in New York, and a tentative diagnosis of epidemic meningitis was made. The spinal fluid cell count was 1,700 per cubic millimeter and practically all of the cells were lymphocytes. Quite obviously it was not meningococcic encephalitis, and a diagnosis of encephalitis was made. We put some spinal fluid into animals and were able to recover a virus without any difficulty.

We saw the other patient in Princeton a week after the onset of his headache. He had a slightly stiff neck. The cell count in the spinal fluid was approximately 750 per cubic millimeter, and without any difficulty at all we also obtained a virus from that spinal fluid. The virus from that spinal fluid turned out to be identical with the virus from the spinal fluid of the first patient. As we studied the virus, we recognized that it was similar to the virus described in 1934 by Dr. Armstrong and Dr. Lillie, in Washington, and similar to the one isolated from normal-looking mice by Dr. Traub in Princeton. Between us we have been able to show that the virus from the patient here in New York, the virus of Dr. Armstrong and Dr. Lillie in Washington, and the virus of Dr. Traub in Princeton are identical.

Just how important this new virus is in regard to human disease we do not know, but there has been described in human beings what is known as acute aseptic meningitis, and there are some indications that a few of these cases are caused by this new virus.

I have just told you about these two cases in order to show that there certainly are other viruses active in the central nervous system of man in addition to those which produce epidemic encephalitis or von Economo's disease and the St. Louis type of encephalitis. As to how many viruses we are going to discover that attack the central nervous system of man and how many viruses are going to be found responsible for the condition we speak of rather loosely as encephalitis, there is no way of knowing at the moment.

Eventually diagnoses in this field are going to be made on the basis of etiology. I do not see how it is going to be possible to place the different kinds of encephalitis in the classifications clinically or pathologically because the same virus can produce different clinical and pathologic pictures in the central nervous system or different viruses can produce the same clinical and pathologic pictures.

Let us suppose you have a case of meningitis, you can make a diagnosis of meningitis, but to say what kind, you must determine the bacteria responsible. You must find out whether it is caused by a pneumococcus, streptococcus, staphylococcus, etc. The same applies to encephalitis. In the individual case, without the use of the laboratory, you cannot tell accurately what kind of encephalitis you are working with. Unfortunately, at the moment, we can only give a laboratory diagnosis on one or two types of encephalitis, the St. Louis type and possibly the new type just recently discovered. There is coming a time, though, when laboratory workers will be able to give the clinician an accurate diagnosis.

CHAIRMAN NEAL.—I would like to make two comments in regard to the question of encephalitis following measles and vaccination. One point is that, while there is no doubt demyelination may be produced in monkeys by the injection of rabbit's brain and therefore that might account for the pathologic picture in the occasional cases of encephalomyelitis that we see following the antirabic treatment, it

would not account for the demvelination in the cases following measles or following vaccine in which no brain substance had been injected. There would have to be some other factor which Dr. Rivers of course, indicated.

Another is that the clinicians who have been working for many years quite unanimously agree that before epidemic encephalitis made its appearance in this country we did not see, except with very rare exceptions, cases of encephalitis following measles or vaccination. The clinical picture is ariesting enough so that had it occurred we hardly could have missed it. I am not trying to give any explanation for these cases following measles but I do entirely agree with Dr. Rivers when he says that he does not think the virus of measles, or of vaccinia, or of chicken por is responsible for these cases of encephalitis. What it can be, whether it is an interreaction of two viruses or just what it is, I am sure I don't know

We will now leave the questions open for discussion

#### DISCUSSION

DR RIVERS -- May I reply to one comment? I did not want to get too deep into this question of demyelination because we are working on it, and I do not want to leid you to believe that we have settled it. You said with regard to measles and vaccinia, etc., no brain material had been injected. We have been going on the assumption that some tissue in the body has been damaged or altered sufficiently by, say, the virus of measles or the virus of vaccinia, or other viruses, that it be comes antigenic for the hemologous host. We took rabbit brain out sterilely, ground it up, and allowed it to autolyze at room temperature Then after it had autolyzed at room temperature, we repeatedly injected that autolyzed brain tissue into rabbits That autolyzed brain tissue paralyzed labbits. We could not find any demyelination in the rabbits, but 30 per cent of the rabbits were paralyzed. Not only were they paralyzed, but they developed antibodies against rabbit brain Fresh rabbit brain taken out and immediately injected into rabbits would not paralyze rabbits and would not produce any antibodies

It is a rather interesting fact that most of the diseases that give rise to perivascular myelination are the ones that attack the skin, e.g., smallpox, chicken pox, measles, vaccinia. The skin is involved, and the skin comes from the same source as does the brain. We have been thinking that it is barely possible that the viruses after the skin in such a manner that the altered skin will then become antigenic for the homologous host and that, inasmuch as the brain and the skin come from the same source, the perivascular myelination might be accounted for in this manner.

DR NEAL -- Why did not our skins react that way in 1910 and 1911?

DR. RIVERS—Of course, there is the host factor. Why is it that one year I only got two paralyzed monkeys out of eight and seven out of eight the next year? There must be a host factor. For some reason or other, genetic or environmental, the human being, the host, is being changed so that now certain things are occurring more frequently than they did previously.

DR CHARLES SCHOTT (CHICAGO, ILL) —What was the difference in the type of cells and spiral fluid in the two cases that were recently observed in Princeton and New York from the ordinary type of encephalitis?

DR RIVERS-I do not know that they were particularly different. They were mainly lymphocytes

DR. SCHOTT - Why are cases of lymphocytic meningitis not encephalitis?

DR. RIVERS —They may be, but Dr. Viets in Boston reported in the Journal of the American Medical Association several years ago that differentiation was made mainly on the clinical picture.

DR. SCHOTT.—Recently the son of one of our colleagues had what was called a lymphocytic meningitis. There was an epidemic of parotitis in the neighborhood at the time although he did not have mumps.

DR. RIVERS.—I have seen here in New York this winter a number of cases with very high cell counts. One of the internes at Columbia had measles and then developed postmeasles encephalitis. He had a cell count of a thousand, which is high for a postmeasles encephalitis. Then we had a patient at the New York Hospital with a cell count of 1,200 I have had many patients with cell counts above 500; in ordinary encephalitis one does not find such high cell counts. Is not that true, as a rule?

DR. NEAL -You will occasionally see high cell counts in encephalitis just as you will occasionally in poliomyelitis, but it is exceptional.

.DR RIVERS.—I believe Dr. Neal can answer this question better than I can, but I will state what I think about these cases of so called acute aseptic meningitis. They have, as a rule, high cell counts; the clinical picture is more of a meningitis than encephalitis; and recovery is slow yet complete so far as I know. The true cases have not the sequelae that follow epidemic encephalitis.

DR. SCHOTT.—In the literature there is evidence that there were cases of en cephalitis following the epidemic of influenza in 1892 and 1893. Is that correct?

DR. NEAL.—I think there probably was more or less encephalitis at that time. I suppose encephalitis can follow influenza just as it can follow other acute infections. In fact, when we first began seeing encephalitis here in the fall of 1918 and the spring of 1919, some of the patients had had influenza, and for a time we thought it was an encephalitis following influenza. Whether encephalitis following influenza has this same picture of demyelination, I do not know.

DR. RIVERS -Greenfield has reported that encephalitis with demyelination occurs at times after influenza.

The important point to remember is that the type of encephalitis cannot be determined regularly by clinical means alone.

DR SCHOTT.—Are the different complications due to a different virus, or is it individual to the patient?

DR. NEAL —That I do not know I am still following one of the first patients with encephalitis I saw here in New York. She has very little in the way of parkinsonism but is very distinctly of the hemiplegic type. When I first saw her, she looked as though she had an early case of tuberculous meningitis.

We have seen all sorts of sequelae or chronic forms following encephalitis in all of the different years. I am sure I do not know whether it is a different etiologic agent or whether it is a different localization of the virus or a different reaction on the part of the patient

DR. RIVERS—Of course, all symptoms that one observes in encephalitis are probably due to the direct or indirect action of a virus on some part of the brain. The location of the activity of the virus rather than the type of virus determines the character of the symptoms in the patient affected.

I can illustrate best by means of some cases of louping ill that I saw in human beings. Louping ill is a meningoencephalitis of sheep in Scotland and northern England. We brought the virus into this country to study its relation to the virus of poliomyclitis.

As a result of working with that virus, a certain number of laboratory people came down with encephalitis. It was rather interesting. One of the individuals had what looked like influenza, came back to work, and then developed a severe headache. He was seen by one of the leading physicians in New York, who made a diagnosis of tuberculous meningitis and gave a very bad prognosis. That patient immediately recovered and is still well.

Another individual had something similar to influenza, came back to work, then developed a severe headache, and went to bed. He was sent to my ward, and Dr. Tilney and I took care of him. We made a diagnosis of epidemic encephalitis, with typical diplopia, sleeplessness at nights, sighing respiration, and gave a very bad prognosis. That patient, immediately after we gave a bad prognosis, began to get well and is now perfectly healthy and has been healthy for two or three years since.

Another individual had a very severe headache and some trouble with the eyes. A diagnosis of influenza was made and the patient made a complete recovery.

Still another individual became sick, and a diagnosis was made of tuberculous meningitis. That individual promptly recovered and is still well.

Thus we have the same virus producing different clinical pictures. Without going into details, I can state that different viruses are capable of causing the similar clinical pictures.

DR. NEAL.—I wish doctors would not make a diagnosis of tuberculous meningitis until they have demonstrated the tubercle bacilli in the smear or until the spinal fluid sugar has become low with a normal blood sugar content.

DR. STERLING II. ASHMUN (DAYTON, OHIO).—I would like to ask your opinion regarding a patient whom I recently cared for, to see whether you think I may have been dealing with an encephalitis of one type and a meningitis of another type in the same individual. This baby was eighteen months old. The doctor had seen him three or four days before admission to the hospital and thought that he had influenza.

He was very stuporous, had a stiff neck and Kernig's sign to a moderate degree. There was no nystagmus or strabismus. There was a very marked bulging of the fontanel. A spinal puncture done immediately showed 300 cells. Since the spinal tap did not relieve the pressure, I made a puncture of the cisterna, which also failed to relieve the pressure as much as I thought it should. By the second day the right pupil had become very markedly dilated and the left was markedly contracted, which fact made me feel that there was a difference in the ventricles.

A ventriculogram, to my surprise, showed the dilated ventricle on the left and a slightly larger than normal ventricle on the right. The child's spinal fluid, in addition, showed a normal or slightly increased sugar. In the successive taps the number of cells dropped from 300 to 50. The child became suddenly worse on the fourth day and died on the fifth day. I was fortunate in securing a postmortem. I should have told you that the blood count was 20,000 white cells with 70 per cent polymorphonuclears. The tuberculin test was negative.

On postmortem examination, we found the brain was not much congested on the surface. The ventricles were as the picture had shown, and in the sylvian tract was a large tuberculous granuloma. Just under the cortex on the left was another tuberculous granuloma as large as my thumb, and in the postcerebral subcortical region was another. We also found a large tuberculous peritracheal lymph gland and the left suprarenal gland completely destroyed by tuberculosis.

Now, that picture as the baby came in was not one of tuberculous meningitis. It was more the picture of lethargic encephalitis following influenza. In the spinal fluid at no time were they able to find the tubercle bacilli, and there was no evidence of miliary tuberculous in the brain. The temperature on admission was not high,

although it had been very high at the onset. The temperature rose, however, to 107° F. before death.

DR. NEAL.—I think that in the presence of tuberculomas one has the picture both in the spinal fluid and in the brain of multiple brain tumors and that the reaction of the tuberculomas and also the increased spinal fluid pressure would be sufficient to account for the child's symptoms resembling encephalitis. Of course, without a generalized tuberculous meningitis, there would be a normal spinal fluid sugar just as with a brain tumor, and probably it would be impossible to demonstrate the tubercle bacilli in the fluid.

DR. BRONSON CROTHERS (Boston).—The situation that Dr. Ashmun speaks of is rather rare, but it is absolutely characteristic, I should think, in certain cases of multiple tuberculous tumors. We have seen it in two cases in which the most searching examination of the spinal fluid was absolutely contradictory to tuberculosis from all points of view. In one case we knew it was tuberculosis, and in spite of that we got blocks in the spinal canal up toward the cerebellum and in the ventricle on one side. We practically demonstrated a diagram with the process, and yet we could not prove a single thing except the pressure relationship was all upset by block.

I would like to know about the criteria of recovery in children after any severe cerebral damage. We make many mistakes in prognosis in these children unless we wait a year from the time the processes come to a stop, and my guess is that a good many of the behavior disorders that follow encephalitis or other cerebral damage are due to a lack of recognition of the influence of the process on the mental equipment of the child. It is probable that we take recovery for granted when we get back to where we were before, without demanding that the child be put on the road to progress at a normal rate.

DR. NEAL.—Yes, I think that is true, and I think you are quite right in saying that a year and even much more must clapse before we can say anything very definite.

DR. JOSEPH STOKES, JR. (Philadelphia).—Dr. Rivers, when the rabbits were injected with their own autolized tissue, how long did it take from final injection until the time that the paralysis developed?

DR. RIVERS.—The rabbits received as a rule about ten injections, two or three a week. They usually became paralyzed toward the end of the course of inoculations or shortly after their completion.

DR. STOKES.—In the case of the Princeton man, was that due to association with Traub's virus?

DR. RIVERS.—I do not know. We have no information in regard to that. All I can say is that our mice in New York, that is, the mice that we have in the Rockefeller Institute, are not infected with the new virus, and the individual here in New York who contracted the disease happened to be a painter who works at the Rockefeller Institute in New York. That virus is not in our stock animals. The virus is in the stock animals at Princeton. As to whether the man contracted it from some individual or from the mice down there, I do not know.

DR. STOKES.—Supposing monkey tissue is injected regularly as it is in vaccinating children against poliomyelitis, do you think that is at all dangerous in connection with the demyelination reaction in human beings?

DR. RIVERS.—In antirable treatment, individuals get 2 c.c. every day for four-teen days. In other words, they get about 28 c.c. of a 4 or 5 per cent emulsion of rabbit brain injected subcutaneously. As I understand it, Dr. Brodie is giving one 5 c.c. dose of a 10 per cent emulsion of monkey brain. In other words. Brodie's

patients are getting one third the amount of heterologous brain as do the people who are vaccinated against rabies. About one person in 4,000, according to the figures given by the report of the League of Nations, vaccinated against rabies comes down with postvaccination demyelinating encephalitis. If one person in 4,000 who gets 28 c.c. of a 5 per cent emulsion comes down and if things work muthematically, about one person in 12,000 or 15,000 might contract a demyelination encephalitis when vaccinated against poliomyelitis. That is purely a guess. Further more, in antirabic vaccination repeated doses are given while Brodie usually gives only one dose.

DR R. M. POLLITZER (GREENILLE, S. C.).—Would it be asking too much if one of you would give us what you consider the minimum basic diagnostic require ments?

DR. NEAL —I will say frankly that I do not know. I do not know any way to differentiate absolutely a nonparalytic type of poliomyelitis from a meningeal type of encephalitis

There are two signs that I place more or less reliance on if they happen to be present. One is that in encephalitis there is quite often an absence of the abdominal reflexes. I know they found this in St. Louis. In poliomyelitis I expect the abdominal reflexes to be normal unless there is a paralysis of underlying muscles which does not occur in a nonparalytic case. The pupillary reflexes are usually normal in poliomyelitis unless there is an extremely increased intracranial pressure which usually is not present, whereas quite frequently in encephalitis there is some disturbance of the pupillary reflexes, either their reaction to light or to accommodation or to both. Thus, I think we can make a diagnosis in which we will be correct in a fairly large percentage of cases of meningeal type of encephalitis with those two symptoms and particularly with some changes in the spinal fluid

Then there are patients who are more or less monosymptomatic—I do not know that this occurs in children so often, I have not seen it at any rate—who will have just diplopin for a while and be able to go about their work although more or less annoyed with disturbance of vision. Some time later a chronic stage develops. Excessive drowsiness or insomnia or reversal of the sleep rhythm or mental disturbances strangely suggest encephalitis. In poliomychitis it is very unusual to see any mental disturbance otherwise than somnolence. Delirium of one type or another is fairly common in encephalitis. Cranial nerve palsies occur in both conditions. I know of no way of differentiating the occasional rare case of the encephalitic type of poliomychitis from an encephalitis, nor the ataxic type of poliomychitis from an encephalitis with ataxic symptoms.

DR. BERMAN S DUNHAM (TOLLDO, O) -How long would the serum be positive?

DR RIVERS—In the St Louis type of encephalitis, the antibodics usually develop rather rapidly, that is, within two or three weeks after the onset of the disease

DR DUNHAM - When does it disappear?

DR. RIVERS—So far as I know most of these patients who develop positive blood signs still retain them. That is true of a number of virus discuses; once you have had a virus discuse, your blood possesses autibodies against it many years afterward, sometimes throughout life. One attack of yellow fever, for instance, will supply you with antibodies in the blood the rest of your life even though you live fifty to seventy years after that attack. That is not true of all virus diseases, however. In poliomyelitis once a person gets antibodies he usually keeps them.

The patients in St. Louis who developed antiviral antibodies seem to retain them. It is rather interesting, however, that some of the patients in St. Louis who had what appeared to be the St. Louis type of encephalitis have never developed anti-

bodies against the St. Louis virus. Now, whether these individuals had something different from the St. Louis type of encephalitis or whether they were people who were incapable of producing antibodies and may have a second attack of the St. Louis type, I do not know.

DR. ALTON GOLDBLOOM (MONTREAL, QUE.).—I should like to discuss a rather interesting group of cases that we have seen in Canada. Both during and out of poliomyelitis seasons children will be brought into a hospital with symptoms resembling poliomyelitis, the only difference being that in most of these cases the spinal fluid findings were entirely negative. In the course of two or three weeks, the paralyses disappeared in spite of the fact that they were complete when they occurred.

Several English writers have referred to this condition as infectious polyneuritis. I should like to ask if this condition might be a virus disease. I have not been quite in favor of accepting this as a polyneuritis because in polyneuritis one would not have central nervous system symptoms such as drowsiness and headache, vomiting, especially the inability to sit up or the inability to bend forward, and Vipond's sign, exactly as one sees in poliomyelitis, but with negative spinal fluid findings and complete and rapid disappearance of the signs.

DR. NEAL.—We do see an occasional case that seems to be poliomyelitis either with or without changes in the spinal fluids, in which the paralysis clears up very quickly. I think most of us have assumed that was because there was very little damage to the cells, just edema, and with the disappearance of edema there was the disappearance of the symptoms. I have seen cases like that but rather rarely. I do not know what I would think if I saw any number of them.

DR. R. C. BOND (WHEELING, W. VA.).—During the last three weeks I have been seeing postmeasles encephalitis.

Two patients were sent into the hospital: one a child, eight months old, in convulsions, and the other with headache, drowsiness, vomiting of sudden onset.

This eight-month-old baby continued in convulsions. Lumbar puncture showed 87 lymphocytes, a blood sugar of 120 mg., a spinal fluid sugar of 35, a negative tuberculin test, and a negative roentgenogram of the chest for miliary tuberculosis. After the convulsions diminished, there was a definite spasticity of the right arm that never did relax.

I thought the child had a case of tuberculous meningitis with the low spinal fluid sugar. Two days later the spinal fluid sugar was down to 30 mg. Later, however, he recovered, apparently, but the involvement of the arm remained. I still think he had tuberculous infection and that we shall see him later.

The other chap was four years old. He was drowsy, listless, and had a stiff neck. He did not respond to questions. The spinal fluid showed 51 mg. of sugar and 10 lymphocytes. The next day we demonstrated a diplopia, a bilateral fourth nerve paralysis, and pupils that failed to react to light. Since the history showed the child had just recovered from measles, I made a diagnosis of measles encephalitis.

The child stayed stuporous and very drowsy for three or four days, but after glucose and repeated lumbar puncture the child made an uneventful recovery and the eye muscles became normal.

A third child was seen on the ninth day of measles. He had been drowsy from Sunday until Thursday, taking no food or water. He could not be aroused. He was stiff, just like a mummy, with cogwheel resistance in both arms and legs. The muscles of his face were immobile. Lumbar puncture revealed 18 lymphocytes and a normal sugar content. He could not talk or swallow.

The neurologic examination revealed a stiff neck, a paralysis of the tenth, eleventh, and twelfth cranial nerves. We could not test smell or hearing. His reflexes were a little hyperactive. He remained very stuporous for about seven days.

On the eighth day he said, "Damn it." After that he started to respond by "uh-huh" if asked a question. At the end of the second week he began to yawn, and he sneezed a few times. He said a few words.

In the last few days he has moved his left leg, and has some grip in the left hand. His face is still masklike, but he will cry a little now. He has become less lethargic and more restless, and sedatives have been used. The cell count in the spinal fluid has never gone above 18. The spinal fluid sugar has been normal.

I wonder about the prognosis of this case and if there is anything more to do than I am doing. I am giving glucose intravenously frequently and am making lumbar punctures every day or every other day. He is getting food high in calories by nasal feedings and mild saline catharties.

Another question is this: Is the severity of sequelae or the chronic state different from that of epidemic encephalitis and is the prognosis just as unfavorable as in epidemic encephalitis? Also I should like to know the relation of the cell count to the severity of the attack.

I had a patient with mumps encephalitis with over 800 cells and two patients with measles encephalitis with over 200 cells, all of whom went on to normal recovery and so far have had no sequelae. Does the lack of cellular response make the prognosis more unfavorable?

DR. NEAL.—I think you are doing everything you can. I cannot tell how long it will take him to recover, or if, indeed, he will. I think there is no definite relationship between the cell count and the severity of the illness except that I think most of us have a general impression that cases with a high cell count, that is, the meningeal type of encephalitis, are likely to be rather less severe and less likely to be followed by the chronic stage.

I think there is no relationship between the severity of the acute attack and the probability of the chronic stage developing. Some of the worst chronic types follow initial attacks so light that they were not diagnosed, while some patients under observation for a long time were very severely ill in the acute stage and have failed as yet, at least, to develop the chronic stage.

The meeting adjourned at 4:50 P.M.

#### Academy News

The following preliminary program has been announced for the Sixth Annual Meeting of the American Academy of Pediatrics to be held Monday and Tuesday, May 11 and 12, at the President Hotel in Kansas City, Mo.

#### Round Table Discussions

Monday, May 11, 9:30 A.M.

Title

Leader

"Asthma"

Francis M. Rackemann, M.D., attending physician, Massachusetts General Hospital, Boston, Mass.

"Childhood Psychiatry"

Franklin G. Ebaugh, M.D., director, Division of Psychiatric Education, The National Committee for Mental Hygiene, New York, N. Y.

"Diagnosis of Appendicitis in Children"

Albert H. Montgomery, M.D., chief surgeon, the Children's Memorial Hospital, Chicago, Ill. "Intestinal Parasitic Infections"

Ernest Carroll Faust, M.D., professor of parasitology, School of Medicine, Tulane University, New Orleans, La.

"Passive Prophylaxis Against Infection in Childhood"

John A. Toomey, M.D., associate professor of pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio.

"Physical Appraisal of the Child"

Alfred H. Washburn, M.D., director, the Child Research Council, Denver, Colo.

"Prophylaxis and Treatment of Whooping Cough"

E. J. Huenekens, M.D., associate professor of pediatrics, University of Minnesota Medical School, Minneapolis, Minn.

"Recent Advances in Nutrition"

W. McKim Marriott, M.D., professor of pediatrics, Washington University School of Medicine, St. Louis, Mo.

"Roentgenology of the Thorax in Children" L. R. Sante, M.D., professor of radiology and director of the department of radiology, St. Louis University School of Medicine, St. Louis, Mo.

"Sinusitis-Indications for Treatment"

L. W. Dean, M.D., professor of Otolaryngology and head of the department of otolaryngology, Washington University School of Medicine, St. Louis, Mo.

"Treatment of the Overweight Child"

L. H. Newburgh, M.D., professor of internal medicine, University of Michigan Medical School, Ann Arbor, Mich.

#### Panel Discussions

May 11, 2:00 P.M.

"Problem of Immunity to Tuberculosis in Childhood"

Chester A. Stewart, M.D., chairman, associate professor of pediatrics, University of Minnesota Medical School.

May 11, 4:00 P.M.

"Cyanosis in the Newborn"

A. Graeme Mitchell, M.D., chairman, professor of pediatrics, University of Cincinnati College of Medicine.

May 11, 8:00 P.M.

Meeting of State Chairmen.

Discussion: "Graduate Education in Pediatrics," Chairman, Borden S. Veeder, M.D.

#### General Meeting

May 12, 9:30 A.M.

President's Address

Scientific Papers

"The Gastrointestinal Portal of Entry in Poliomyelitis," John A. Toomey, M.D.
"The Clinical Application of the Blood Coagulant Extract Obtained From the
Human Placenta," R. Cannon Eley, M.D., and Charles F. McKhann, M.D.

#### Consideration of Reports

(Reports will be presented in mimeograph form to the membership.) Report of the Executive Board. Report of the Secretary-Treasurer. Report of Regional Committees Report of Special Committees New Business. Installation of New President

On May 12, at 2 P M, the Round Table Discussions will be repeated.

Dr. William B. McClure, of Evanston, Ill., died suddenly of heart disease on February 13.

#### News and Notes

The following men have been certified by the American Board of Pediatrics since the last report.

- Dr Harry Bakwin, New York, N. Y.
- Dr. Ruth Morris Bakwin, New York,
- Dr. Granderson Hearn Bradly, Nashville, Tenn.
- Dr. Floyd S Clarke, Omaha, Neb
- Dr. Wyman C. C Cole, Detroit, Mich.
- Dr. Harry Hampton Donnally, Washing ton, D. C.
- Dr James Everett Dyson, Des Moines, Iowa
- Dr. Fred Leib Glascock, Los Angeles, Calif.
- Dr. Alton Goldbloom, Montreal, Canada
- Dr. Philip C. Jeans, Iowa City, Iowa Dr Edgar J. Huenekens, Minneapolis,
- Minu. Dr. Sigurd Herbert Kraft, Chicago, Ill.

- Dr. George Marshall Lyon, Huntington, W. Va.
- Dr. Kathanne Krom Merritt, New York, N. Y.
- Dr Walter Roger Moore, St. Joseph, Mo
- Dr. Lillian Lydia Nye, St. Paul, Minn
- Dr. Martin D Ott, Davenport, Iowa
- Dr. Marshall Carleton Pease, New York, N. Y.
- Dr. Bennett Watson Roberts, Durham, N. C.
- Dr. Lester Rosenberg, Brooklyn, N. Y.
- Dr. Roland P. Seitz, San Francisco, Calif.
- Dr Morton Seldowitz, Brooklyn, N. Y.
- Dr. Warren Richards Sisson, Boston, Mass.

The American Board of Pediatrics will conduct the following examinations-

Kansas City, Mo, on May 9, preceding the meeting of the American Medical Association and the American Academy of Pediatrics

Albany, N. Y., on June 10, preceding the meeting of the American Pediatrics Society

Baltimore, Md. in November, 1936, at the time of the joint meeting of Region I and Region II of the American Academy of Pediatrics

Cincinnati, Ohio, in November, 1936, at the time of the Region III meeting of the American Academy of Pediatrics

San Francisco, Culif, at the time of the Region IV meeting of the American Academy of Peliatrics Date as yet unannounced

The next meeting of the Society for Pediatric Research will be held at the Chalfonte-Haddon Hall, Atlantic City, N. J., on May 5, 1936. The president is Dr. Chirles F. McKhann, and the secretary is Dr. A. Weech, New York

The next meeting of the Section on Pediatrics of the American Medical Association will be held in Kansas City, No, on May 13, 14, and 15, 1936

The American Pediatric Society will hold its annual meeting at Hotel Sagamore, Bolton Landing, N. Y., on June 11, 12, and 13, 1936. Dr. Fritz B. Talbot is president, and Dr. Hugh McCulloch, secretary. Immediately following the meeting of the Society there will be held exercises for dedication of the Abraham Jacobi Memorial. Further announcement of these exercises will be made later.

The annual meeting of the South Carolina Pediatric Society was held at the Francis Marion Hotel, Charleston, S. C., January 28, 1936. Dr. Wilbert C. Davidson, dean of the medical school of Duke University, was the principal speaker. The following officers were elected:

Dr. L. B. Salters, Florence, S. C., president

Dr. Hilla Sheriff, Spartanburg, S. C., vice president

Dr. D. Lesesne Smith, Jr., Spartanburg, S. C., secretary and treasurer

The next meeting of the South Carolina Pediatric Society is to be held in Columbia, S. C., in November, 1936.

A meeting of the Beardsley Pediatric Club of Connecticut was held at the State School for Boys at Meriden, February 13, 1936. Dr. Charles I. Soloman, pediatrician-in-charge, presented several cases illustrating the personal and social aspects of juvenile delinquency with special consideration of the behavior and personality changes of children with organic brain disease, such as encephalitis, epilepsy, and cerebral trauma.

#### Correspondence

London, February, 1936.

Comment has previously been made upon the report of the British Medical Association's Committee on Nutrition. In September, 1935, a booklet entitled "Feeding, Meals, and Catering" was published by the Association. This is in effect a small cookery book based upon the dietary previously recommended for a man, wife, and three children, and is meant essentially for the housewife to whom economic considerations in the feeding of the family are of the first importance. This little booklet is to be welcomed, and has obviously had a very wide appeal, judging by the considerable sale that appears to have followed its publication. It is undoubtedly a great help to those concerned to be supplied with suitable menus in which variety is introduced, even though what at first sight appear to be an unappetizing list of foodstuffs have to be principally employed, for the sake of cheapness.

In November, 1935, meetings were taking place in London of the expert Committee on Nutrition appointed by the Health Committee of the League of Nations, and its report has recently been published. Broadly speaking, their conclusions are of a nature already generally accepted by all concerned in nutritional work and in the scientific feeding and care of children.

Not so long ago considerable anxiety was expressed in some quarters lest children here should be suffering from the results of industrial depression. The Board of Education issued a report which was reassuring, though this was not accepted everywhere. Reports during 1935 continued to be satisfactory, the total figure for malnutrition increasing only by approximately 1 in 1,000; there is, however, striking

dissimilarity in nutritional states from area to area, and from class to class. In London the percentage of subnormal nutrition in 1035 is said to have been lower than ever before.

In this country, school care committees and head teachers select children for free meals, and a scheme also exists for the provision of free milk

The milk scheme introduced in October, 1934, caused an increase of no less than 256 per cent of those receiving milk for payment and 110 per cent of those receiving it free. It is interesting to note that it is reported that the failure to buy milk at school was caused by poverty in 25 per cent of cases only, that 33 per cent dis liked milk, and that in another 24 per cent of cases sufficient nourishment was considered to be obtained at home. There are more than twenty areas in which local education authorities are making provision for free milk during school holidays, and in a few cases also during the week ends in term time

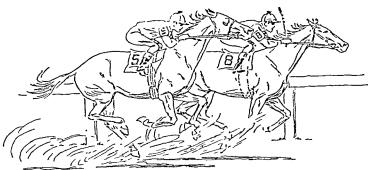
In relation to nutrition it is interesting to consider the findings of Dr. A. G. Watkins, who carried out a survey of the physical condition of children between the ages of three and five years in Cardift and Rhondda schools. These two areas, situated in Wales, differ, the latter coming under the official designation of "distressed area" Watkins's paper, which is worth attention, was published in the British Medical Journal in June, 1935. His main conclusions are (1) that there is no single cause of malnutrition; (2) that malnutrition is not common in the areas examined; (3) that endogenous factors have a greater immediate effect on the health than evogenous factors; (4) that an unsatisfactory economic state probably tends to promote the occurrence of all health, and to prevent adequate convalescent environment and nourishment.

The Board of Education has just issued a circular, giving its views on the development of physical education in the schools and among young people generally. It is of importance and interest to note the attention being paid by public authorities to such methods of training for the purpose of attaining physical fitness in the young members of the community.

The annual report of the Chief Medical Officer to the Board of Education, Dr. Arthur McNalty, has just been published, and will doubtless be referred to by those interested in such aspects of paediatries, but at any rate one point raised seems worth mentioning here. In discussing dental care, an enquiry in certain districts into children naturally free from dental caries revealed only one safe generalisation, that the regular use of the toothbrush is not essential for freedom from caries. Of 560 children with sound teeth recorded, 104 brushed their teeth irregularly, and 132 never! The dictetic habits of these children gave most be wildering results, all soits of dictetic errors had been indulged in by those whose teeth were perfect.

The list meeting of the British Paediatric Association was held for the first time in Ireland, at Newcastle, County Down, and proved a tremendous success. A resume of the proceedings was published during the summer in the Archives of Discase in Childhood, and will not therefore be again detailed here. This year's meeting is to be held in England, at Windermere in the Cumberland Lakes District, under the presidency of Dr. Naish of Sheffield; it will take place early in May

The annual meeting of the British Medical Association is being held in July, and this year is taking place at Oxford. Dr R Jewesbury is President elect of the Children's Section, whose programme includes discussions on the subjects of wasting in infancy and obesity in childhood. In view of the delightful surroundings this year's meeting should be particularly attractive, and no doubt there will be a very large attendance.



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## Die Hautkrankheiten des Kindesalters

(Band X "Handbuch der Kinderheilkunde" 4, Auflage) Mit 383 zum grossen Teil farbigen Abbildungen. XIII, 884 Seiten. 1935 RM 169 .-: in Halbleder gebunden RM-178.

Inhaltsübersicht: Allgemeiner Teil: Anatomischer Aufbau der Haut im Kindesalter. Von Professor Dr. J. Becker, Bremen. — Stoffwechsel und Immunbiologie der Haut. Von Professor Dr. P. György, Cambridge (England). — Allgemeine therapeutisch-technische Hinweise. Von Geh. Rat Professor Dr. L. v. Zumbusch, München. — Spezieller Teil: Angeborene Fehlbildungen der Haut. Von Dr. K. Steiner, Wien. — Geschwülste der Haut. Von Professor Dr. W. Scholtz, Königsberg. — Pigmentanomalien, Xantome und Schüller-Christiansches Syndrom, Recklinghausensche Krankheit. Von Privatdozent Dr. W. Jadassohn, Zürich. — Hautveränderungen bei Leukämien, Lymphogranulomatose und Erkrankungen verwandter Art. Von Professor Dr. O. Ullrich, Essen. — Hautveränderungen bedingt durch Störungen am peripheren Geffensteller Von Professor Dr. O. Stein, Wien. — Anomalien r. R. O. Stein, Wien. — Anomalien r. R. O. Stein, Wien. — Anomalien r. R. O. Stein, Wien. — Anomalien und Erkrankungen des Talg. und Scholtz, Wien. — Herpes. Von Dozent Dr. H. Lehndorff, Wien. — Ekzem und ekzemähnliche Dermatosen. Von Geh. Rat Professor Dr. H. Finkelstein, Berlin. — Ekzem und ekzemähnliche Dermatosen. Von Geh. Rat Professor Dr. H. Finkelstein, Berlin. — Erkrankungen der Haare und Nägel im Kindesalter. Von Professor Dr. C. Moncorps, München. — Die Epidermolysis bullosa — Dr. J. K. Mayr, Münster. — Keratosen. Von Professor Dr. C. Stein, Wien. — Psoriasis vulgaris. — Lichen ruber. Von Professor Dr. O. Kiess, Leipzig. — Haut-Diphthetie. — Vaccinosen. — Exanthematische Formen der Hautschalten in Zusammengestellt von Dr. Erna Eckstein-Schlossmann, Düsseldorf.

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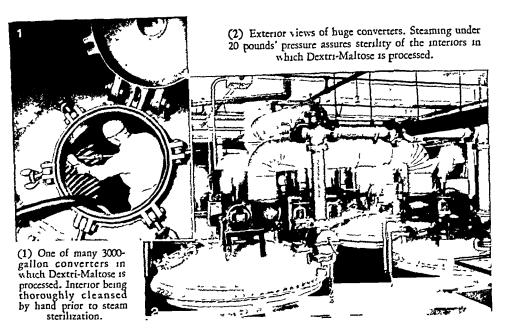
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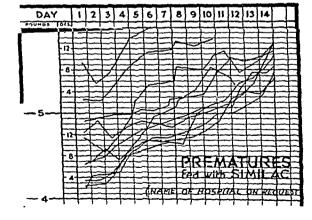
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\*Holt, Tidwell and Kirk, Studies on Fat Metabolism in Infants-Acta Pediatrica, Vol. XVI, 1933.

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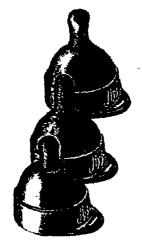
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- \*Diseases of Infancy and Childhood, New York, Appleton-Century, 1933.
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- \*\*\* Feeding and the Nutritional Disorders in Infancy and Childhood, Philadelphia, Davis, 1928. The Infant and Young Child, Philadelphia, Saunders, 1929.

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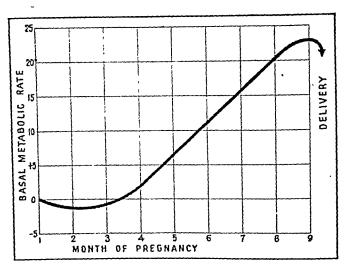
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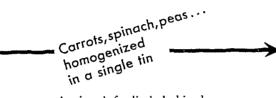
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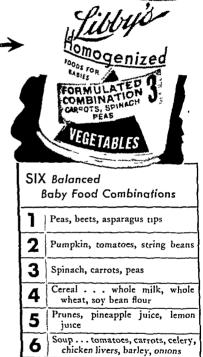
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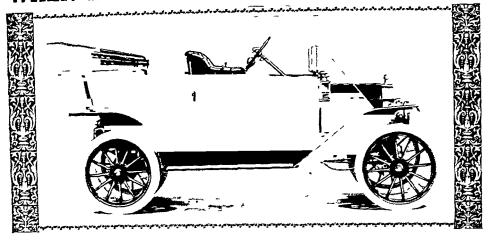
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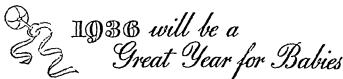




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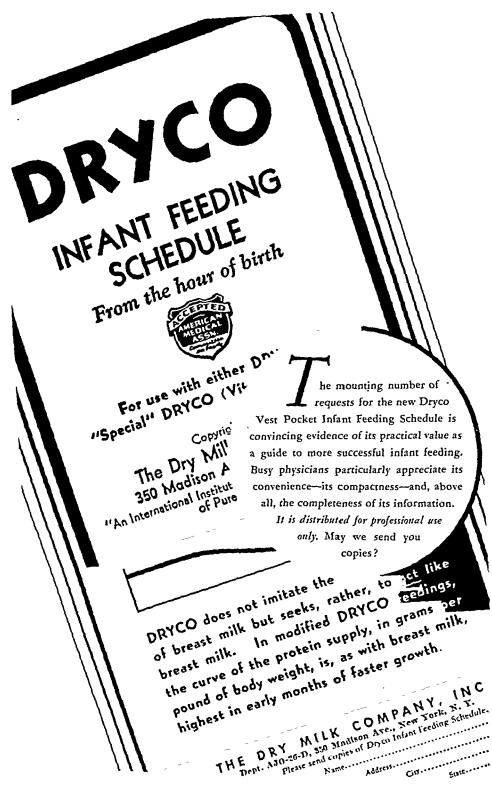
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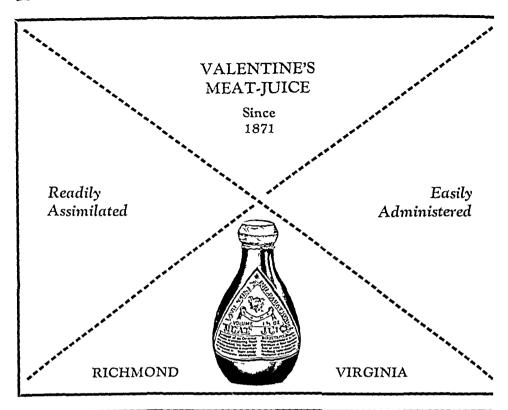


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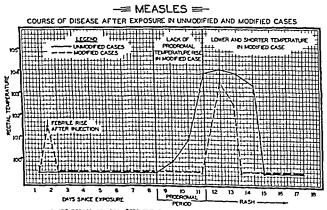
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# The Journal of Pediatrics

Vol. 8

FEBRUARY, 1936

No. 2

#### Original Communications

THE USE OF A BLOOD COAGULANT EXTRACT FROM THE HUMAN PLACENTA IN THE TREATMENT OF HEMOPHILIA

R. CANNON ELEY, M.D., ARDA ALDEN GREEN, M.D.,
AND CHARLES F. McKhann, M.D.
WITH THE ASSISTANCE OF ISRAEL KAPNICK AND HARRIET F. COADY
BOSTON, MASS.

R ECENTLY Sakurai called attention to the fact that the action of "placental toxins" in bringing about the coagulation of blood was similar to the coagulants which have been made from animal tissues (Wooldridge, Loeb, Howell, Mills and others). This investigator extracted fresh human placentas with 0.9 per cent NaCl solu-The slightly opalescent suspension of material obtained by centrifugation was effective in shortening the coagulation time of recalcified oxalated blood plasma of rabbits and dogs. The toxicity of the extract for animals was found to run parallel to the coagulant power. The activity was weakened or destroyed by oxidation, heat. proteolytic enzymes, and long exposure to air. The active principle was globulin-like in nature and contained 1.226 per cent phosphorus. When injected into the veins of animals in large amounts, it defibrinated the blood and at the same time was exercted into the urine with its coagulant power retained. The oral or subcutaneous administration shortened the coagulation time of the blood of animals in vivo and in vitro.

The purpose of this communication is to record observations on the effectiveness of a tissue protein prepared from human placentas in the treatment of hemophilia. Studies have also been made in an attempt to determine similarities or differences in the coagulating action on the blood of this preparation with other animal tissue extracts.

Before describing the technic which we have employed in preparing this extract, it is important to emphasize the distinction between

From the Department of Pediatries, Harvard Medical School and the Children's and Infants' Hospitals.

This study was supported in part by a grant from the Commonwealth Fund of New York.

this blood coagulant fraction of the human placenta and the antibody solution ("placental extract immunizing" or "immune globulin" [human]) described by McKhann and his associates used for prevention or modification of measles and containing antibodies for poliomyelitis, searlet fever, and diphtheria. The immunizing antibodies in the placenta may be prepared from placental serum as well as from repeated saline extractions of the organ. On the other hand, the blood coagulant fraction is definitely a protein derived from the placental tissues since placental serum contains but negligible quantities. The blood coagulant is a very insoluble globulin being easily precipitated in isotonic saline at pH 5. The antibodies for virus diseases (poliomyelitis) are found in this and all other globulin fractions. The antitoxins (scarlet fever and diphtheria) are found in the more soluble pseudoglobulin fractions made from extracts of the placenta.

#### PREPARATION OF BLOOD COAGULANT FROM HUMAN PLACENTA

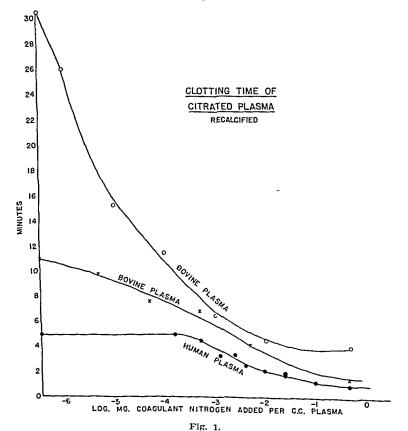
Placentas obtained from nonsyphilitic and nontoxic women were used. When possible, all operations were carried out in a cold room. The placentas were ground in a food chopper and extracted with ice-cold isotonic saline solution. A second extraction was made with distilled water rendered slightly alkaline so that the hydrogen ion concentration of the extract was about 8.5. The extractions were made by agitating the material for thirty minutes, and then filtering through cheesecloth. The extract was centrifuged to remove red cells and solid material and was then acidified with 0.1 N hydrochloric acid to pH 5 (blue green to bromeresol green after dilution with water). The heavy flocculant precipitate, which settled out readily on standing, represented the coagulant fraction. The precipitate was washed twice with water to remove the hemoglobin and salt and was taken up in distilled water and weak NaOH until the pH was about 7.5. Then 0.2 per cent NaIICO, was added and the pH readjusted to 7.5. Onehalf per cent tricresol was added as a preservative although this does not guarantee sterility. The nitrogen concentration of the final solution should be between 2 and 3 milligrams per cubic centimeter. supernatant fluid from this isoelectric precipitation could be used for the preparation of placental extract for immunizing purposes ("immune globulin human'').

The placental extract possessing coagulant activity was a turbid material of brownish color, which could not be put into true solution. It was precipitated in an acid medium, was difficultly soluble in dilute alkalies, and rapidly lost its potency in alkaline or acid solutions. The activity was greatly impaired by passage of the extract through Berkefeld or Seitz filters. The active material was also removed from suspension by passage through a Sharples centrifuge. The activity was destroyed by oxidation and by aging, particularly in the presence of fresh blood serum.

Since the placental extract does vary in its coagulant activity, it has been found necessary to check its potency frequently so that none but reasonably active extracts are used clinically.

The potency of the placental coagulant may be tested in vitro by its effect on the clotting time of recalcified, citrated, bovine plasma. At least 0.3 per cent sodium citrate is added to bovine blood and the plasma removed by centrifugation. The plasma may be kept in the cold for two or three weeks if 1:5,000 merthiolate is added.

One cubic centimeter samples of the plasma are pipetted into small test tubes which have been thoroughly cleaned and rinsed with iso-



tonic saline before use. The plasma is allowed to come to room temperature. One-tenth of a cubic centimeter of the coagulant to be tested is added to the plasma. To this and to a control tube is added 0.3 c.c. of 2½ per cent calcium chloride. The time necessary to form a solid clot is ascertained. Determinations should be made in duplicate. Temperature, acidity, and calcium chloride concentration materially influence the coagulation time and should be carefully controlled.

If the control clots in fifteen minutes, the tube to which coagulant has been added should clot in two or three minutes. If the control

time is longer—for example, thirty minutes—the coagulant should clot the plasma in less than 5 minutes if it is to be regarded as sufficiently potent for use.

#### EFFECT OF BLOOD COAGULANT

When tested, it was found that the extract, when added to drawn, fresh citrated blood, shortened the congulation time. Furthermore, the potency of the congulant factor was found to be present even when the extract was employed in dilutions as high as 1:10,000. The relation of the concentration of the blood congulant extract to the congulation time of recalcified plasma is shown in Fig. 1, and from this it can be seen that the congulation time of both bovine and human plasma is reduced in the presence of the placental congulant extract.

As it has been suggested by Mills<sup>5</sup> and Loeb<sup>3</sup> that tissue coagulants may possess some degree of specificity for the species from which they are derived, in vitro studies were made with recalcified, eitrated blood plasma from animals and humans. The reduction in the coagulation time of the human plasma was more marked when the placental coagulant extract was added. Similarly, the bovine lung extract was more effective in coagulating bovine plasma. Both extracts were made simultaneously in an identical manner and were of the same protein concentration. (Table I.) This would suggest some degree of species specificity and that human tissue extract might be more effective when employed as a coagulant in human beings.

TABLE I

COAGULATION TIME OF RECALCIFIED HUMAN OR BOVINE CITRATED PLASMA TO WHICH
BOVINE LUNG COAGULANT EXTRACT OR PLACENTAL COAGULANT
EXTRACT HAS BEEN ADDUB

		TIME OF CONGULATIO	N
	CONTROL	LUNG EXTRACT ADDED	PLACENTAL EX- TRACT ADDED
Human plasma A	9'56"	1'45"	1'10"
Human plasma B	10'23"	2'01"	1'19"
Human plasma C	10'50"	2'05"	1'24"
Human plasma D	9'10"	2'08"	1'35"
Bovine plasma A	14'25"	1' 0"	2'10"
Bovine plasma B	19'45"	1'45"	3'05"
Bovine plasma C	12'35"	1'25"	2'36"
Bovine plasma D	13'29"	1'10"	2'18"

To 1 c.c. of plasma was added 0.1 c.c. congulant extract (containing 1.5 mg. N per c.e.) and 0.3 c.c. 2.5 per cent CaCl<sub>2</sub>.

Observations on the coagulation time of both the venous and capillary blood were made in rabbits by the intraperitoneal injection of 1 c.c. amounts of the extract. The coagulation time of the venous blood was determined by placing 1 c.c. amounts of blood obtained from the heart by a syringe into each of three tubes. The first tube was tilted at short intervals until coagulation was noted. The second

and third tubes which were not agitated clotted more slowly. mean of the second and third tubes was taken as the coagulation time. The coagulation time of the capillary blood was determined by the method of Petersen and Mills8 using capillary tubes. The results showed that there was a prompt reduction in the coagulation time of the blood of rabbits as obtained from the heart and as obtained by pricking the ear. This reduction persisted for periods varying between forty-eight and seventy-two hours. Following the administration of large doses of placental extract in animals, Sakurai noted the development of a negative phase, i.e., a period of time during which the blood was rendered noncoagulable. Such a phase did not occur in our animals with the dosage which we employed. The reaction of the animals varied according to the mode of administration of the extract. Intravenous injection into rabbits, guinea pigs, and monkeys resulted in death of the animal from intravascular coagulation, whereas subcutaneous, intramuscular, or intraperitoneal injections in small dosages were not lethal but shortened the coagulation times of both capillary and venous blood for variable periods. Large doses had a slowly toxic effect on all of these animals. The character of this toxic effect will be considered in a subsequent communication.

As the effectiveness of the material in reducing the coagulation time of the blood in animals had been demonstrated, it seemed desirable to note its effect in man. Therefore, after having determined the coagulation time of both the venous and capillary blood, 5 c.c. of the extract was administered orally to a normal individual after the manner as suggested by Mills<sup>5</sup> in the use of bovine lung extract. Thirty minutes later determinations of the coagulation time of both venous and capillary bloods showed that the clotting time of the venous blood had been reduced from six and one-half minutes to one and one-half minutes and that the clotting time of the capillary blood had fallen from two and one-half to one and one-half minutes. Examinations of the blood were then made at hourly intervals, and at the end of five hours it was observed that the coagulation times had returned to the normal levels. The duration of the effect in the normal human individual was thus found to be the same as Mills had observed under similar conditions following the use of bovine lung extract.

#### OBSERVATIONS ON PATIENTS WITH HEMOPHILIA

When in vitro comparisons were made between the blood of normal individuals and the blood from patients with hemophilia, it was found that the blood of the latter group coagulated just as rapidly and effectively as that from the normal group.

Fifteen patients suffering from hemophilia have been given the blood congulant extract prepared from human placentas in order to determine the effect of the human tissue substance on the congulation time of the capillary and venous blood. In this series of cases the blood congulant extract has been administered in two ways, orally and intramuscularly.

The oral administration of the extract has been preceded by a period of fasting in order to lessen various digestive enzymes in the stomach which tend to destroy the coagulant factor. For this reason it has usually been given before breakfast and preceded and followed by a small glass of ice cold water as this accelerates gastric motility. In view of the recent observations concerning the influence of oil of peppermint on the emptying time of the stomach, we have added a few drops of the oil to the material at the time of ingestion. The extract has also been given orally in sodium bicarbonate and in alkaline carbonated water, and it would appear that it may be more readily absorbed from one of these mediums than from ice water. After the ingestion of the material it is advisable to allow from three to four hours to elapse before anything else is taken by mouth. Older children and adults, particularly, have seemed more resistant to the administration of the extract by mouth than have younger children.

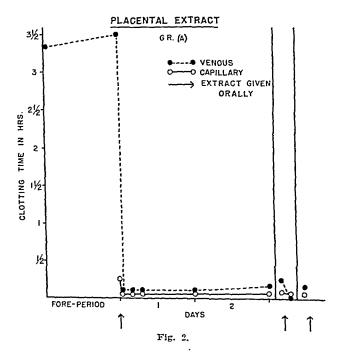
The intramuscular injection of a sterile form of the blood coagulant extract has been employed only in those patients who have failed to show any response to oral administration. The gluteal region has been the usual site of the injection, and in no instance has it been followed by a reaction that would contraindicate its use in this manner. Care should be exercised when the extract is injected as it may produce intravascular coagulation should any of the material be given intravenously.

When administered orally, the effectiveness of the coagulant factor can usually be demonstrated within fifteen to twenty minutes by a reduction in the coagulation time of both the venous and capillary blood. The response following intramuscular injection, however, is slow, and several hours may be required before the full effect of the extract can be noted.

The dosage and frequency of treatment cannot be stated in a categorical manner as these may vary with each patient. In these studies we have given usually 5 e.c. orally, and, if there is no response, the amount is gradually increased by 5 c.c. until 15 to 20 c.c. are given. If there is still no response, from 10 to 15 c.c. are given two or three times in one day. Should the patient prove refractive to the oral administration, 5 c.c. of the extract are then given intramuscularly. In the majority of instances this dosage is adequate although on occasions it has been found necessary to inject 10 c.c. before a satisfactory response could be demonstrated. When more than 5 c.c. are given intramuscularly, it is advisable to inject the material into two sites. The duration of the effect of the extract, whether administered

orally or intramuscularly, varies with the individual patient. Therefore, in order to determine the frequency with which the material should be given, the coagulation time of both the venous and capillary blood should be noted each day. In this manner the time at which the coagulation time tends to return to its former level can be determined.

Eleven of the fifteen children with hemophilia who have been treated have shown a satisfactory response to either the oral or intramuscular administration of the extract as evidenced by a reduction of the coagulation time to within ten minutes, which we have taken as the upper limit of normal. Although in the other four instances there was a reduction in the coagulation time, the end point was not sufficiently



low for us to consider the effect as satisfactory as in the other group of cases. The effect of the blood coagulant extract by oral and intramuscular administration is shown in Table II. S. C. (Case 6) failed to respond to the oral administration but showed a prompt reduction in the coagulation time when the extract was given intramuscularly. It will be noted in Cases 11 and 14 that, although there was a marked reduction in the coagulation time, we were unable to reduce it to within normal limits. It should be pointed out that patients with hemophilia may show a variable response to the extract. This was especially true in Patients 2. 9, and 10 (Table II). This was probably due to a delayed emptying of the stomach or the result of poor absorption of the extract from the gastrointestinal tract.

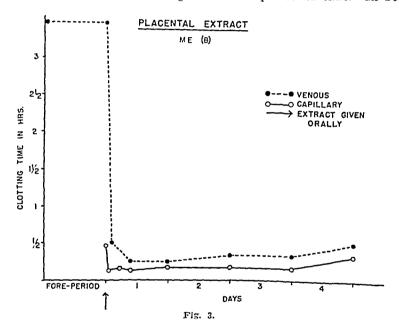
Tabe II Heman Placental Teste Grobulds: Effect in Patients With Hemophilia

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COAGULAT	AFTER TH	CAP.	3.30	,05,4	4.20,		"Uest		7.	: 2	1	"Uini.	5.20"	40016	770	3.30	10,	8,12,,	à i	10,	7,	10,10,	.01.6	201	2	1 1 1 1	1	1	10,	11.50.	11	10,	17'20"
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r days	13,	10, -,	3,30,	33,	10.0	Oral with earbon.	17	1/19/35	M. E.	1

In Figs. 2 and 3 the reduction in the coagulation time of the capillary and venous blood when the extract was given orally with cold water is illustrated. Fig. 4 shows an immediate response when extract was given in cold alkaline carbonated water after there had been no response when the substance was given in plain cold water.

Inasmuch as large doses of placental extract in animals may result in a phase during which the blood is noncoagulable, the question has arisen whether or not the placental coagulant extract can be administered repeatedly over a long period of time without danger to the hemophiliac patient. The reports of two cases in detail will illustrate the amounts which have been given over a period of time. In both



of these patients, ingestion of the extract at proper intervals has permitted the child to lead a normal, active life, despite minor cuts and abrasions which previously had been incapacitating.

Case 1.—(Case 1, Table II.) G. R., a white male child, eleven years old, was first admitted to the hospital at the age of two years on account of prolonged bleeding from the tongue. The patient had bitten his tongue, and bleeding had persisted in spite of local applications of various hemostatic agents. Three blood transfusions were necessary to control the hemorrhage. The family history showed that one maternal aunt had had a male infant who died with hemorrhages and that a second male child had a marked tendency to develop hematomas and to bleed profusely following slight trauma. The past history of the patient revealed that black and blue spots or raised bumps were easily produced by any type of injury. In view of the family history, clinical course, and hematologic studies, a diagnosis of hemophilia was made.

From November, 1930, until December, 1934, the patient was treated by protein sensitization as advocated by Vines and Mills. During this time he appeared to be slightly improved although he continued to develop hematomas and hemarthroses from trauma and to bleed from loose, carious teeth.

Since December, 1934, the patient has received the placental coagulant by mouth in doses of 5 c.c. twice a week. The effect of a dose of extract by mouth is shown in Fig. 2. Frequent determinations of the coagulation time of both the venous and capillary blood throughout this period have shown them on each occasion to be within normal limits. In a period of seven months the child has received by mouth 650 c.c. of placental tissue coagulant without untoward effect. The clinical course has been uneventful, and quite in contrast to previous years which had been marked by the development of hematomas following slight trauma. On account of the ease with which hemarthrosis occurred, the patient had been unable to enjoy the usual activities of a child. During the past seven months he has participated in various forms of school activities, obtained a bicycle, and has enjoyed the usual

# EUNG AND PLACENTAL EXTRACTS RS. VENOUS O CAPILLARY EXTRACT GIVEN ORALLY DAYS DAYS FORE-PERIOD A B FIG. 4.

winter sports of his locality. On one occasion he pierced his tongue with a fork, producing four puncture wounds. This accident was not followed by hemorrhage. Formerly the loss of a carious tooth was accompanied by prolonged bleeding from the cavity, but this winter such unpleasant features have been absent.

Case 2.—(Case 8, Table II.) M. E., a white male child, was first admitted to the hospital when thirteen months old, on account of a marked tendency to develop ecchymotic areas and to bleed profusely after slight trauma. There was no family history of hemophilia. Following circumcision at one week of age, he bled profusely and had required several blood transfusions. Thereafter he showed a tendency to bleed for prolonged periods following slight trauma. The coagulation time of both the venous and capillary blood was prolonged. A diagnosis of hemophilia was made. Since the age of fifteen months the patient has received placental coagulant in a dosage of 5 c.c. by oral administration at various intervals—usually five days. The effect of the material by mouth is shown in Fig. 3. Throughout a period of eight months the coagulation times of both the venous and capillary blood have approached normal limits, and the patient has been free from hemorrhage, although

on two occasions he has suffered from lacerations of the face. Small ecchymotic areas have occurred occasionally. This child has received over 250 c.c. of placental congulant during this period.

As the result of the experience with these two patients, it seems quite likely that the placental blood coagulant may be taken without detriment over a considerable period of time by the hemophiliae patient. However, before drawing too definite conclusions on this point, it will be necessary to obtain information on a larger series of cases. Whether a toxic effect would follow repeated doses in the normal person has not been satisfactorily established.

Whether or not the blood coagulant extract which reduces the coagulation time in hemophiliacs for periods as long as five to nine days will have an effect in arresting internal hemorrhages in these patients remains to be seen.

While the data herein reported are suggestive, they do not answer definitely the question as to whether the homologous nature of this coagulant renders it superior to the animal tissue coagulants now available. Mills was able to shorten the coagulation time of the blood in hemophiliae patients by the oral administration of bovine lung tissue extract, but this shortening was of only a few hours' duration. The brief duration of the effect of lung extract has been confirmed by trial of a commercial preparation of lung extract as well as by bovine lung tissue coagulant prepared in our own laboratory (Table III). The results with a heterologous protein derived from bovine lung tissue are in sharp contrast to the more prolonged effect following the administration of the homologous tissue extract derived from the human placenta.

TABLE III

ROVINE LUNG TISSUE GLOBULIN: EFFECT IN PATIENTS WITH HEMOPHILIA

NAME	NAME DATE METHOD OF ADMINISTRATION		DOSAGE IN C.C.	COAGULAT	TION TIME PERIOD VEN.	COAGULAT AFTER TR	DURATION OF EFFECT	
R. Sp. M. E.	2/2/35 2/20/35 2/20/35 5/10/35 5/16/35	Oral Oral Rectal	5 5 5 20 5	6'30" 15' 15' 13' 12'	1°40' 2°30' 40'	4'45" 6'20" 10' 13' 10'30"	40' 1°40'	6 hours 3 hours No effect

The potency of the blood coagulant extract when applied to the tissues locally has been noted in the treatment of normal individuals following traumatic injuries and certain postoperative hemorrhages, notably bleeding following tonsillectomy and adenoidectomy. The local action of placental tissue extract in a patient with hemophilia is illustrated in the following case report.

Case 3.—R. S., a known hemophiliae child, was admitted to a neighboring hospital because of a laccration of the scalp which was bleeding profusely. Despite a

transfusion and the local application of various commercial thromboplastic substances, the bleeding from the wound continued for three days. At the end of this time a piece of cotton saturated with placental extract was placed firmly over the wound and within five minutes coagulation occurred without subsequent oozing.

#### SUMMARY

Tissue protein extracts prepared from the human placenta have been found to have the same type of effect in the control of local hemorrhage as has been reported from the use of animal tissue extracts. However, a striking difference has been observed in the results with this extract and those reported from the use of animal tissue preparations in the treatment of patients with hemophilia. Animal tissue extracts have shortened the coagulation time of the blood of patients with hemophilia for very\_brief periods, whereas human placental extracts have reduced the clotting time of both venous and capillary blood for periods varying from forty-eight hours to as long as nine days. Despite repeated slight trauma incident to active childhood, two children with hemophilia have been able to lead normal, active lives for periods of several months by the continued administration of this material at carefully regulated intervals.

In the relatively small series of patients with hemophilia herein reported, the blood coagulant extract has been well tolerated by oral administration or by intramuscular injection. It must be emphasized that this blood coagulant extract is fatal when injected intravenously in small laboratory animals. Therefore, in using this material in patients with hemophilia, intravenous injection must be avoided as by this route unfortunate, if not fatal, results might ensue.

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#### ACUTE LYMPHOCYTIC MENINGITIS?

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Y ATTENTION was first attracted to this disease by its rapid spread in an orphanage which housed 360 male children from three to sixteen years of age and sixty-five adults. The first child to become ill with the symptoms to be described later was admitted to the hospital cottage on Aug. 1, 1935, and within twenty-one days a total of seventy children had been hospitalized (Chart 1). symptoms and signs exhibited were so unusual and so strikingly similar that they may be grouped in the order of their importance as follows: (1) Headache: This was marked and always present. most cases it was frontal in position and often so excruciating that drugs did not afford relief. It was aggravated by motion, and when the patients were in a standing position they sometimes became dizzy. (2) Anorexia With Nausca or Vomiting: All seventy children had at least anorexia and nausea, while the majority vomited as well. children had diarrhea. (3) Sore Throat: Many of the children complained of sore throat of varying severity. Although this condition did not seem to trouble them, objective examination showed that there was involvement of the pharyngeal wall of every patient, ranging from a diffuse inflammatory reaction to localized spotty points of inflammation. Islands of minute lymphoid tissue jutted out from the pharyngeal wall and soft palate. Only a few children had cervical lymphadenopathy. Four patients had herpes labialis. gastric Pain: Every child had pain when light or deep vertical palpation was employed in the epigastric region roughly corresponding to Mackenzie's area of referred pain for duodenal ulcer. At least one half of the children had more diffuse pain, and this was found always in the midline between the ensiform cartilage and the umbilicus. (5) Temperature: The highest temperature recorded was 104.3° F. and the lowest 99° F., while the average was from 100° to 101° F. In one case, the temperature became normal in two days; in 42 cases, in three days; in 12 cases, in four days; in 10 cases, in five days; in 4 cases, in six days; and in 1 case, in seven days. (6) Pain Over the Eyes: About twelve of the patients had pain on palpation of the eyeball, and twenty complained of subjective pain in the eyes. Spinal Fluid Findings: In one child with an intractable headache

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unrelieved by medication, the spinal fluid was withdrawn as a therapeutic procedure. The headache disappeared following this therapy. The fluid contained 180 cells per cubic centimeter, all of which were lymphocytes, and the Pandy test was negative. Another puncture was done on this boy the next day. The results were comparable. In all, lumbar punctures were made on eighteen patients. All but

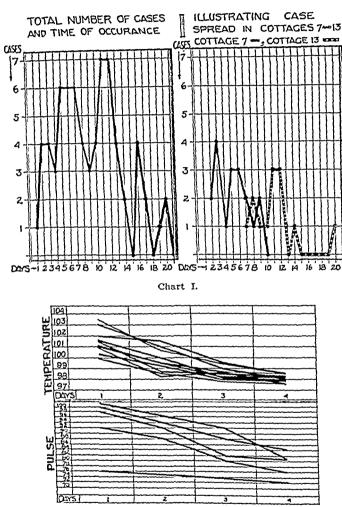


Chart 2.—Temperature in ten and pulse in five cases of lymphocytic meningitis.

two children who had the disease for five days had pleocytosis of the lymphocytic type. In one instance, the lymphocytes merely predominated in the first spinal fluid specimen withdrawn. The cell counts ranged from 25 to 350 cells per cubic centimeter. The Pandy reaction was usually negative, and at best, only faintly positive. This finding was so curious that fresh Pandy solutions were made and the spinal fluids tested again Spinal fluids that contained as many as 180 cells showed but a faint trace of globulin. When the cell count was higher than that, the Pandy reaction could be read as a possible This was probably due to the cellular elements one-plus reaction themselves rather than to any free globulin fraction. In decided contrast, four-plas Pandy reactions are often found in the spinal fluids of tuberculous meningitis cases-fluids that have a low cell count. In a recent case of postvaccinal encephalitis with a cell count of only 21, the reaction to the Pandy test was four-plus when only one drop of the solution was added to the spinal fluid. It was found that the pleocytosis was not always present the first day of the disease, but invariably on the second or third day, usually when the child was better clinically. (8) Blood Picture: Total white and differential blood counts were made in the eighteen cases mentioned above. The total counts were low, ranging from 3,200 to 5,000. Only one was abnormally high. In ten of the eighteen cases there was a relative lymphocytosis, the latter cells being nearly as numerous as the leucocytes and sometimes outnumbering them. Sample lymphocyte counts from four cases were 58 per cent. 64 per cent, 67 per cent, and 72 per cent of the total white cell counts. These patients were nine, seven, eleven, and seven years of age, respectively. (9) Culture of the Throat on Blood Agar: Not all cultures were taken at the onset of the illness, but a hemolytic streptococcus was isolated in each of ten of the eighteen cases mentioned above, i.e., cases cultured early. Throat cultures taken from a comparable number of children throughout the village were negative for hemolytic streptococcus. (However, in thirty subsequent cases seen elsewhere, only five cultures showed hemolytic streptococci on blood agar plates.) (10) Neurologic Examination: Because of the headaches, all of the children were examined neurologically. In no instance was there any sign of meningeal irritation, although at times there was pain in the neck when the head was forcibly flexed on the chest and some subjective pain in the back. The normal reflexes were not modified nor were pathologic ones present. No sign of muscular weakness was present.

Clinical Course.—The disease was explosive in character, and the patients were well within a few days after the onset. There were no complications or sequelae. In a few cases, headache persisted for several days.

Second Attacks.—Two boys were readmitted with the same symptoms a few days after their first release from the hospital.

Adults.—Five of the sixty-five adults living in the orphan home contracted the disease. They showed symptoms and signs similar to those had by the children. Lumbar punctures were not permitted.

Contagiousness.—The contagiousness of the disease is obvious when the case spread in cottages 7 and 13 is studied (Chart 1).

Other Cases.—This epidemic was not a local one, for I have seen thirty other cases with the same symptoms in widely separated areas of Cleveland. In two cases in which lumbar puncture was permitted, the spinal fluid findings were likewise similar. Isolated cases with the same symptoms and signs have been seen in previous years, but information on the blood smears and spinal fluid findings is lacking save for one patient seen in 1934, who had findings similar to those seen in the epidemic described here. Higher white counts (from 8,000 to 10,000) have often been found in the second group of thirty cases mentioned, but irrespective of this, in most instances there was a relative increase in the number of lymphocytes Twenty-five cases that might have been similar to ours have been seen by Currier, fourteen by Ashton, and fifty-five cases of a peculiar poliomyelitis without paralysis have been noted by Lucchesi 3

Treatment.—Each patient was given a cathartic, a liquid diet, and put to bed for four or five days. If patients got up before this time, they often had a return of the headache Codeine or, in severe cases, lumbar puncture controlled the headache.

Discussion -These cases might have been (a) types of encephalitis, (b) abortive poliomyelitis, (c) a form of infectious mononucleosis (Glanzmann<sup>4</sup>), (d) acute aseptic meningitis of Wallgren,<sup>5</sup> benign lymphocytic choriomeningitis of Armstrong and Dickens,6 benign meningitis of Rivers and Scott,7 or (e) a new disease syndrome. could not have been encephalitis since there was absolutely no subjective or objective signs of this disease—no diplopia, no tic, no evidence of an upper motor neurone response, no hyperactive reflexes. no lost abdominal reflex, etc It could not have been poliomyelitis or polioencephalomyelitis since no child showed any muscle weakness or paralysis, any diminution or modification of the reflexes-abdominal, tendon, or otherwise. One would expect to find at least some lower motor neurone findings if all these cases were poliomyelitis. our series of nearly 700 cases of poliomyelitis, there were but few patients who had any objective evidence of throat involvement, while all of these children had involvement of the lymphoid tissue in that Convalescent serum withdrawn from five of the patients during convalescence from the disease showed no increase in neutralizing antibodies for the poliomyelitis virus when the M. rhesus monkey was used as the test animal. Although no virus could be found in the nasal washings of eight children, this does not rule out the presence of a virus as the causative factor.

This syndrome might have been a form of infectious mononucleosis, as there are records of spinal fluid pleocytosis of large mononuclears in

the latter disease, but ordinarily, patients who contract it do not have intractable headaches. Likewise, the syndrome described in this paper showed no glandular enlargements.

These cases might be placed in the same category as those described by Wallgren,<sup>5</sup> later by Viets and Watts,<sup>8</sup> Armstrong and Dickens,<sup>6</sup> and Rivers and Scott.<sup>7</sup> The one distinctive difference is that most of the cases described here presented a blood picture that is not found in acute aseptic meningitis. The causative factor of aseptic meningitis has been shown by Rivers and Scott,<sup>7</sup> and Armstrong and Lillie,<sup>9</sup> to be a filtrable virus, which was found to be similar to the one found by Traub<sup>10</sup> in mice. One wonders whether Kessel's<sup>11</sup> virus strain may not belong in the same category.

It would seem that the lack of glandular enlargement, the finding of spinal fluid pleocytosis, and the changes in the blood picture would be distinctive enough to label this entity a new syndrome, and I had tentatively termed it "acute epidemic lymphocytosis," but then again it may be that I have merely seen a more severe form of acute lymphocytic meningitis or more cases of this known entity, all the characteristics of which hitherto have not been described.

#### COMMENT

The minute lymph follicles of the throat were definitely swollen. The disturbance of lymphocyte cell count, always present in the severely ill patient, was striking enough to warrant the inclusion of the word lymphocytosis in any name given to the syndrome. It could not be said that all of the children had sore throats since less than half of the children were conscious of the condition of their throats, while those who did complain of angina were better within twentyfour hours. The pain in the epigastrium was obvious enough, but like the headache was probably secondary to the original cause of the This disease could be visualized as an infection entering the human system by way of the gastrointestinal tract, irritating the throat tissue in passage and later the gastrointestinal tract itself and causing anorexia with either nausea or vomiting or both, local pain, and headache due to irritation of the peripheral ends of the sympathetic and vagus nerve fibers-a disease that in a certain percentage of cases causes a relative increase in the number of circulatory lymphocytes. Whether there are actual inflammatory changes in the meninges, or whether there is a vascular defect with increased permeability which allows lymphocytes to pass over into the spinal fluid are questions that remain unanswered. Of significance, however, is the absence or small amount of protein elements in the spinal fluid in the majority of these cases.

#### CONCLUSION

This paper describes an epidemic of a disease, the symptoms of which are excruciating headache; anorexia with nausea or vomiting or both; pain in the epigastrium on palpation; a low grade fever; a throat moderately or severely inflamed; some pain on movement of the head; a total white count, perhaps lower than usual, but if normal, in most eases, with a relative increase in the circulatory lymphocytes; negative neurologic signs; a spinal fluid pleocytosis with lymphocytes predominating in the severely affected case; and a hemolytic streptococci that was easily isolated from the throats of a small percentage of the cases. It would seem that this may be a new syndrome or a more severe manifestation of acute aseptic meningitis. It should be kept in mind and differentiated from poliomyelitis.

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## THE ANTIRACHITIC VALUE OF IRRADIATED EVAPORATED MILK AND IRRADIATED WHOLE FLUID MILK IN INFANTS

(AN IN-PATIENT STUDY)

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THIS study was carried out to gather further data concerning the prophylactic antirachitic value of directly irradiated evaporated milk and of irradiated whole fluid milk, both similarly rendered antirachitic and containing approximately the same number of rat units of vitamin D. In a previous study we have reported that irradiated evaporated milk "appeared to be an adequate agent for the prevention of rickets in negro infants" and that "it also appeared to be an unreliable agent for the cure of rickets in negro infants." Gerstenberger and his associates2 have demonstrated that irradiated milk will produce healing of the rachitic bony changes fairly regularly in from ten and one-half to eleven weeks. We are convinced that vitamin D-fortified milks will not find their greatest usefulness in the cure of rickets if it takes as long as eleven weeks to effect this cure, an end which may be obtained much more rapidly using some of the more potent available sources of vitamin D. Consequently we have concerned ourselves more with the prophylactic value of irradiated milks.

The evaporated milk and the whole fluid milk used in this study were both directly irradiated. Assays of the evaporated milk both at the beginning and end of the study showed that it had a vitamin D content of 125 U.S.P.\* units per 14.5 ounce can and that there was no change in the vitamin D content over the period of the study. The fluid milk was assayed at monthly intervals throughout the study and found to have a fairly constant vitamin D content of about 140 U.S.P.† units of vitamin D per quart.

Nineteen infants were selected for this investigation. These were all white infants, under twenty-four weeks old. Table I shows the age distribution of the infants. All were free from evidences of syphilis and tuberculosis. An attempt was made to select nonrachitic infants, but it was found that one infant had mild rickets, and two infants had questionable x-ray evidences of very mild rickets at the beginning of the study.

From the Children's Hospital of Philadelphia.

<sup>\*45</sup> Steenbock units.

<sup>150</sup> Strenbock units.

	TABLE	T	
Age	DISTRIBUTION	OF	Infants

AGE IN WK.	NO. OF INFANTS
1 - 4	2
$\begin{array}{ccc} 5 \sim & 8 \\ 9 \sim & 12 \end{array}$	3 8
13 ~ 16 17 ~ 20	2 1
21 - 24	ĩ

Fourteen of the infants were kept in a large isolated hospital ward during the entire period of the study. The remaining five infants were housed in a small isolated ward for two months and were then discharged because it appeared impossible to prevent cross-infections. Three of the five were followed as out-patients at weekly intervals, but two lived too far from the hospital to permit of their frequent returns.

The in-patients were not taken outdoors, and, since the study was carried out from December, 1934, to May, 1935, the antirachitic effect of the sunlight coming through the glass windows of the ward was practically negligible.

Complete histories, physical examinations, blood counts, and urinalyses were performed on each infant at the beginning and end of the study. Measurements of length, circumferences of head, chest and abdomen, and sizes of fontanelles were recorded at monthly intervals.

Muscular development and tonus, time of eruption of teeth, sitting, standing, and walking were recorded as evidences of physical development. Each infant was weighed daily and a record of daily milk intake was kept. At monthly intervals physical examinations were made for evidences of rickets. At the same time as the physical examinations, blood was withdrawn for the determination of the calcium and the phosphorus contents, and roentgenograms of an arm and leg were taken. The roentgenograms were read by Dr. Ralph Bromer, roentgenologist to the Children's Hospital, and independently by the authors.

The infants were divided into two groups: one group of ten infants was placed upon irradiated evaporated milk, and nine infants were given irradiated whole fluid milk. The ten infants receiving irradiated evaporated milk were in the ward during the entire period of study, while of the nine infants fed irradiated whole fluid milk, four were in the ward during the entire study (four and one-half months) and five were on the ward for only two months.

The feeding schedule employed was the following: the irradiated evaporated milk was diluted equally with water, and 5 per cent of

dark corn syrup was added. Five per cent dark corn syrup was also added to the undiluted irradiated whole fluid milk. These milk mixtures were offered to the infants on the basis of 55 calories per pound of expected body weight. Cereals and vegetables were added to the dietary when an infant attained the age of six months. Two antiscorbutic agents were fed, a different one to alternate infants in each of the two groups, viz., orange juice and cevitamic acid. Two and five-tenths cubic centimeters of orange juice were fed per pound of expected body weight. The cevitamic acid was dissolved in 10 per cent dark corn syrup so that each ounce contained 10 mg. of the acid. This was also fed in quantities of 2.5 c.c. per pound. Ferric ammonium citrate was added (2 per cent) to both the orange juice and the cevitamic acid solution.

TABLE II

LACK OF AGREEMENT BETWEEN CLINICAL AND ROENTGENOGRAPHIC

EVIDENCES OF RICKETS

IN-	AGE (MO.) AT TIME	1	AL SIG		X-RAY EVID.	(A	00D .V.)	
FANT	OF	CRANIO-	ING	MENT	OF	VAL	UES	COURSE OF INFANT
	DIFFER- ENCE	TABES	OF RIBS	OF WRISTS	RICKETS	CA	P	
С	2.5	Moder- atc	0	0	0	11.1	5.5	Craniotabes d is a p- peared entirely by 6 mo. Never any other rachitic phenomena. Development normal.
D	3-7	0	Mild	0	v	10.3	7.7	Beading appeared after 1 mo. on ward. Did not progress. No other evidence of rickets. Development normal.
J	4-7	0	Mila	0	0	10.9	6.3	Beading noted after 2 mo. on ward. Did not progress. No other evidences of rickets. Development normal.
P	3-5.5	0	Zild	0	0	11.5	7.4	Beading noted on ward. Did not progress. No other evidences of rickets. Develop- ment normal.
v	3,5-4,5	0	Mild	0	0	11.2	6.5	Beading noted after 3 mo. on ward. Did not progress. No other evidences of rickets. Development normal.

#### RESULTS

For reasons which we have pointed out in our previous study, we again used the roentgenographic evidence of rickets as our final criterion of the presence or absence of rickets. In five of the infants there were present some clinical signs of rickets while roentgenographic bone changes indicative of rickets were absent (Table II). In these five infants the blood calcium and phosphorus values were normal at the time the clinical signs were noted.

In Table III are summarized the results in the ten infants who were fed irradiated evaporated milk. Two of these infants (J and M) had very questionable rachitic bone changes at the beginning of the study, the remaining eight (C, D, F, G, K, O, P, and V) were free from rickets. After one month roentgenograms showed that all were non-rachitic, and the entire group remained normal for the entire period of the study, four and one-half months. During this time blood calcium and phosphorus values were all normal, and physical development and growth were satisfactory as Table III shows.

In Table IV are summarized the courses of the nine infants who were fed irradiated whole fluid milk. Four of these infants (E, N, Q, and R) were in the ward the entire four and one-half months and remained free from rickets during the entire period. Two infants (L and X) were on the ward for two and one-fourth and two and one-half months, respectively, and because they were only three months old on discharge the data concerning them may not be as significant. However, they at no time exhibited any rachitic phenomena. Their physical examinations, roentgenograms, and blood calcium and phosphorus values were normal. Of the three infants who were on the ward for two months and out-patients for two and one-half months or more. two (H and T) had no evidence of rickets at any time. On admission one of these three infants (S) had a mild rickets which began to heal (by roentgenographic evidence) in thirteen weeks and was healed at the end of the study. At the time when the bones showed rachitic changes by roentgenogram and there was a moderate craniotabes, the blood calcium and phosphorus values were normal. Hess and his coworkers3 have pointed out, however, that the blood calcium and phosphorus concentrations could be normal in the presence of mild rickets. While healing was complete in this infant after eighteen weeks, it took thirteen weeks before healing was initiated.

The administration of iron did not seem to influence the hemoglobin level significantly in any of the infants.

Both antiscorbutic agents, orange juice and cevitamic acid, functioned equally well in preventing scurvy, as far as we could determine from physical examination and roentgenograms.

Table 111
Infants on Irradiated Evaporated Milk

DEVELOPMENT		Well developed. Sat up at	Sat up at 54 mo. Had 6 teeth at 6 mo. Stood with	Support at 1 mo. Could sit up and had 2 teeth at 6 mo.	Stood unsupported and had	Sat up at 5½ mo. Had 2 teeth at 7 mo.	Sat up at 5½ mo.	Sat up at 6 mo. 2 teeth at 6 mo.	Had 2 teeth at 6 mo. Stood	Sat up at 54 mo.	Sat up at 4½ mo. Well developed
BLOOD CHEMISTRY (AVERAGE)	à	5.6	6.4	7.0	6.7	6.5	6.7	6.4	6.3	7.4	6.8
CHEN	CS	11.2	10.1	11.2	10.7	10.8	11.2	10.4	10.5	11.3	10.9
ABSENCE OR PRESENCE OF	RICKETS	No evidence of rickets at	nny time No evidence of rickets nt 10.1 any time	No evidence of rickets at	No evidence of rickets at 10.7	Very questionable x-ray change at 2 mo. Normal	thereafter No evidence of rickets at 11.2	Vory questionable x-ray change at 3 mo. Normal	thereafter No evidence of rickets at	No evidence of rickets at	any time  No evidence of rickets at 10.9 any time
AVERAGE INTAKE OF VIT. D	PER DAY U.S.P. UNITS	104.0	118,0	128.0	139.0	112.5	119.5	121.6	130.2	128.0	129.0
OVIN IN	INCHES	£1-	5£	13	ĸ	ស	33	33	33.3	+61 10	es
GAIN IN	WEIGHT	4 lb, 10 oz.	7 lb.	5 lb. 10 oz.	6 lb. 12 oz.	7 lb. 14 oz.	s lb.	7 lb. 3 oz.	6 lb. 13 oz.	8 lb.	5 lb. 12 oz.
	MO, ON WARD	<b>*</b>	7	7	÷	~T*	÷.	47	- <del></del>	- <del></del> 7	+
TIME STUDIEL	MO.	===	 	<b>{</b> †		₽ <del>-</del>	-47 -77	#	-47	÷	<b>+</b>
	AGE	2-64	t- G1	23-7	18·1·	£-01	2.63	3.73	3.73	1-5}	1-1
i żi	FANT	ြ	2	Ŀ	C	۲,	×	×	0	ď	>

Table IV

		DEVELOPMENT		Had 2 teeth and sat up	at 6 mo.	Sar up at 5 mo.	44	Sat up at 6 mo. Had 2	Sat up at 6 mo.	In and	Had 4 teeth and could	Sat up at 54 mo. Had 2	teeth and stood up at	8 mo.		Had 2 teeth at 5 mo. Sat	up at 51 mo.	Well-developed intant	
		ISTRY LAGE)	а	6.8	,	<u>ခ</u>	6.8	<b>6.4</b>	÷	;	5.7	y	?			7.	1	5.0	
		CHEMISTRY (AVERAGE)	CA	10.9		10.0	11.3	11.0	t.	7.01	10.0	0 01	9.01			11.2		11.4	
LUID MILK		ABSENCE OR PRESENCE	OF BUNETS	No omidones of rickets at	any time	No evidence of rickets at	No evidence of rickets at 11.2	any time No evidence of rickets at 11.0	any time	No evidence of rickets at 10.1	No evidence of rickets at 10.9	any time	On admission had cranio-	dence of mild rickets.	Beginning healing 13	WK. Regied in ## mo. No evidence of rickets at	any time	No evidence of rickets at 11.4 any time	
INFANTS ON IRRADIATED FLUID MILK	AVERAGE	INTAKE OF VIT. D	PER DAY		727	1001	105	120.5		136	145		136			118		114	
FANTS ON		GAIN IN LENGTII	INCHES		<del>-}</del> i	71	11	44	•	O	7	ı	44			=======================================	fre #I	er F	
ž		GAIN IN	WEIGHT		5 lb. 4 oz.	6 lb. 11 oz.	2 lb. 5 oz.	É	· 101	7 lb. 12 oz.	11, 0 0%		7 lb. 11 oz.			7	6 10. 11 0Z.	3 lb. 4 oz.	- [
			0.P.D.	MO.	0	ಣ	0		>	0		>	157					0	-
		TUDIED	WARD	(MO.)	77	¢1	61	; ;	#1 #	1	· ;	## 1 ## 1	C.3				¢.1	-F-2	-
	,	TIME ST		М0.	17	ls.	, rt	i ·	47	4	1 :	<b>47</b>	‡				4.4	Ę.	
				AGE	24.7 mo.		7.0 110.	1.94 mo.	2-6} mo.	0.61 mo.		51-10 mo.	34-8 mo.				1-54 mo.	4-3 mo.	~
		<b> </b>	-NI	T.V.V.T	民	: :	≓ ,	7	Z	c		r:	ďΩ				Ęų	ĸ	-

#### DISCUSSION

From the data presented in Tables III and IV, it would appear that irradiated evaporated milk containing 125 U.S.P. units per 14.5 ounce can and irradiated whole fluid milk containing 140 U.S.P. units per quart, functioned equally well in preventing rickets when they were the sole source of vitamin D in the diet. The slight difference in vitamin D content is obviously of no significance so far as the protection afforded the infants in the two groups is concerned since the infants fed irradiated evaporated milk had an average daily intake of 123.9 U.S.P. units of vitamin D daily and those on irradiated whole fluid milk took 122.4 U.S.P. units daily. The variations in the vitamin D intake of the infants in the two groups were as follows:

Irradiated evaporated milk-104-142.5 U.S.P. units daily. Irradiated whole fluid milk-100-145.0 U.S.P. units daily.

The slow healing of mild rickets in patient S by means of irradiated whole fluid milk emphasizes a fact which was evident in a larger group of a previous study:1 namely, that a milk which contains approximately a minimum number of units of vitamin D for the protection of most infants (when it is the sole antirachitic source) will act as a slow, and therefore unsatisfactory, healing agent.

Proper therapeusis, or rapid healing, probably requires an antirachitic potency greater than either of the two sources here studied.

#### CONCLUSION

There are presented the results of a study of nineteen white infants (averaging two months in age) to determine the prophylactic antirachitic value of irradiated evaporated milk containing 125 U.S.P. units of vitamin D per 14.5 ounce can, and of irradiated whole fluid milk containing 140 U.S.P. units per quart.

No roentgenographic evidences of rickets developed during the period of study, four and one-half months.

The irradiated evaporated and whole fluid milks appeared to be equally efficacious in preventing the development of rickets.

In one infant in whom mild rickets was present at the beginning of the study, healing began in thirteen weeks and was complete in eighteen weeks. It should be emphasized, therefore, from this and previous studies, that irradiated milk alone cannot be relied upon for the rapid healing of rickets.

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## IRRADIATED EVAPORATED MILK IN THE PREVENTION OF RICKETS

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RRADIATED evaporated milk is now being used extensively in both the United States and Canada. Rapoport, Stokes, and Whipple¹ in a recent report concluded that irradiated evaporated milk seemed to be an adequate agent for the prevention of rickets. In this test which extended over a period of four and one-half months, actively growing negro infants living in a hospital were used, and all the milk that they received was irradiated evaporated milk. The presence or absence of rickets was diagnosed by x-ray examination. No other investigations on the antirachitic value of this milk have as yet been reported.

During the past year we have investigated the value of irradiated evaporated milk in the prevention of rickets. One hundred and three infants attending the infant welfare clinics in Toronto were observed for a period of five months. The observations were started in October and November and concluded in March and April. The infants all lived in their own homes, and the parents were largely of British descent. The milk feedings, which consisted of irradiated evaporated milk, water, and sugar only, were regulated by the clinic physicians. The amount of irradiated evaporated milk used varied from 6 to 20 ounces daily, depending on the caloric requirements of the infant. although very few of them received more than 16 ounces. At five to six months of age cereal was added. During the last month of the period of observation, five infants received egg yolk. The ages of the infants at the initial examination in October and November varied from one to six months (Table I). Seven of the infants had been premature, their birth weights ranging from 3.2 to 4.7 pounds.

TABLE I

AGES OF INFANTS IN MONTHS AT TIME OF INITIAL EXAMINATION

GROUP	UNDER 1 MO.	1 мо.	2 мо.	3 мо.	4 мо.	5 мо.	6 мо.	TALS
Irradiated evaporated milk	0	19	20	24	17	19	4	103
Ordinary evaporated milk	1	12	10	14	7	6	2	52
Ordinary pasteurized milk	0	7	12	16	9	7	1	52

From the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children.

Three times during the five months the infants attended a special clinic at the Hospital for Sick Children for physical and x-ray examination. The infants were weighed and carefully examined for evidences of craniotabes, costal beading, epiphyseal enlargement, and bowing of the legs. Practically all the infants gained weight faster than the usual rate. X-ray films were made of both wrists at each examination. The feedings of the infants were checked, and the mothers were instructed that no source of vitamin D other than the irradiated evaporated milk was to be given. A special nurse visited the homes to see that all instructions were accurately carried out. Excellent cooperation was obtained throughout, and of the 113 infants selected in the fall we were able to follow no less than 103 during the whole five winter months.

In addition, we were able to observe fifty-two infants of the same age fed ordinary evaporated milk and fifty-two infants fed ordinary pasteurized milk (Table I). Incidentally during the period of these observations no irradiated evaporated milk was available commercially in Toronto. None of these infants received any vitamin D. During the last month of the period only one infant received egg yolk. Of the fifty-two infants fed ordinary evaporated milk two were premature, and of the fifty-two infants on ordinary pasteurized milk one was premature.

The irradiated evaporated milk used throughout this observation was prepared in one lot and stored until used. The milk was assayed for its vitamin D content at periodic intervals and a constant value of 9.8 international vitamin D units per ounce was found. This vitamin D content was the same as that found in ordinary commercial irradiated evaporated milk. The vitamin D assay was carried out on rats, and, in order to compensate for the calcium and phosphorus present in the milk, the vitamin D assays were made by comparing the antirachitic effect of a measured amount of the irradiated evaporated milk with 2.1 times this amount of ordinary fluid milk to which a known amount of international standard vitamin D had been added. The ordinary evaporated milk which we used was found by animal assay to give no evidence of any extra vitamin D, when compared with ordinary fluid milk.

After the final x-ray films were taken, they were examined for the presence or absence of rickets. The authors are greatly indebted to Dr. Martha Eliot, Children's Bureau. Washington, D. C., for the interpretation of all the x-ray films. The degree of rickets was classified by Dr. Eliot as 1-, 1, 2 and 3. In this paper we have called Dr. Eliot's Group 1- extremely slight rickets (a barely perceptible change which frequently might not be noted); Group 1, mild rickets (a slight

but obvious rachitic change); and Groups 2 and 3, moderate and marked rickets (well-defined fringing and cupping at the end of the bone). The interpretation of the x-ray plates was made without any knowledge of the antirachitic material administered.

Again as noted in a previous communication<sup>2</sup> and as confirmed by Rapoport, Stokes, and Whipple,<sup>1</sup> we were unable to find any constant relationship between the x-ray evidence of the presence or the absence of rickets and the clinical signs. From these observations it would appear that when dealing with a large group of patients under home conditions, it is only by x-ray examination that the presence or absence of rickets can be determined.

In Table II is given the incidence of rickets as shown by x-ray films at the initial examination in the autumn. In the interpretation of the x-ray from the clinical standpoint it must be kept in mind that the "extremely slight rickets" are so slight that most physicians would classify these x-ray plates as "normal." Those grouped as "mild rickets" also do not show changes which would cause any great concern from the clinical standpoint. In contrast to this, the "moderate" and "marked" cases with well-defined fringing and cupping at the ends of the bones are of definite concern to the practicing physician. It is to be noted that in the group fed ordinary pasteurized milk there happened to be at the initial examination a few more patients with mild rickets than in the other groups. However, these numbers, when considered with the final numbers in Table III, are not great enough to affect the conclusions drawn.

TABLE II

CASES WITH EVIDENCE OF RICRETS ON INITIAL EXAMINATION IN AUTUMN

GROUP	TOTAL NUMBER OF CASES	EXTREMELY   SLIGHT RICKETS	VILD RICKETS	MODERATE AND MARKED RICKETS
Irradiated evaporated milk	103	20	1	0
Ordinary evaporated milk	52	9	1	0
Ordinary pasteurized milk	52	4	4	0

In Table III is shown the effectiveness of irradiated evaporated milk as compared with ordinary evaporated milk and ordinary pasteurized milk in the prevention of rickets. Of the 103 infants who were fed irradiated evaporated milk none developed moderate or marked rickets, while 10 per cent of those fed ordinary evaporated milk, and 23 per cent of those fed ordinary pasteurized milk developed rickets of this degree. We have no explanation of the fact that fewer infants developed moderate and marked rickets on ordinary evaporated milk than on ordinary pasteurized milk. In addition, only 17 per cent of the infants fed the irradiated evaporated milk developed mild rickets

whereas 29 per cent of those fed the ordinary evaporated milk and 25 per cent of those on the ordinary pasteurized milk showed mild degrees of rickets.

TABLE III

THE EFFECTIVENESS OF IRRADIATED EVAPORATED MILK IN THE PREVENTION OF RICKETS AS EVIDENCED BY X-RAY FILMS:

MAXIMUM DEGREE OF RICKETS OBSERVED AT ANY TIME SUBSEQUENT TO INITIAL EXAMINATION

GROUP	TOTAL NUMBER OF	SLI	EMELY GHT SETS	1	(LD KETS	MODERATE AND MARKED RICKETS		
	CASES	NO.	%	NO.	%	NO.	%	
Irradiated evaporated milk Ordinary evaporated milk Ordinary pasteurized milk	103 52 52	20 S 2	19 15 4	18 15 13	17 29 25	0 5 12	0 10 23	

The x-ray films were also interpreted by Dr. Eliot on the basis of the activity of the rachitic process. For this classification the x-rays showing evidences of rickets were divided into three groups, Group A in which the rachitic process was active and showed no evidence of healing; Group B in which there was definite evidence of lime salt deposition in the rachitic process; and Group C in which the rachitic process was healed. It should be noted that this classification indicates only the state of activity of the rachitic process and does not indicate in any way the degree of rickets. In Table IV is shown the activity of the rachitic process at the times of observation. The results are rather striking. In the group receiving irradiated evaporated milk, whenever there was any evidence of rickets present, there was always evidence of healing as shown by lime salt deposition. On the other hand, in the groups receiving ordinary evaporated milk and ordinary pasteurized milk in many of the infants with "mild rickets" there was no evidence of healing.

TABLE IV

ACTIVITY OF THE RACHITIC PROCESS AT TIMES OF OBSERVATION

**************************************	\ 		UTUMN	<u> </u>	MIDDL	E OF W	INTER	END	OF WI	NTER
group	TOTAL	THE PARTY	HEAL- ING RICK- ETS		ACTIVE RICK- ETS	HEAL- ING RICK- ETS		ACTIVE RICK- ETS	HEAL- ING RICK- ETS	CURED RICK- ETS
Irradiated evaporated milk	103	10	11	0	0	3.5	1	0	22	12
Ordinary evaporated milk	52	3	7	0	ŋ	13	0	10	10	3
Ordinary pastcurized milk	52	ō	3	0	12	s	0	17	7	0

#### SUMMARY

- 1. The antirachitic effect of irradiated evaporated milk was observed on 103 rapidly growing infants, aged one to six months at the initial examination. The infants, who were largely of British descent, were observed during the five winter months. The entire milk requirements of these infants were supplied by irradiated evaporated milk, and no other source of vitamin D was administered. "Moderate" or "marked rickets" as shown by the x-ray examination did not develop in a single infant. Seventeen per cent of the infants showed x-ray evidence of "mild rickets," a degree of rickets that is not sufficient to cause any great concern from a clinical standpoint.
- 2. Fifty-two infants of similar ages whose entire milk requirements were covered by ordinary evaporated milk were observed over the same period. Of these, 10 per cent developed x-ray evidence of "moderate" or "marked rickets," and 29 per cent developed x-ray evidence of "mild rickets."
- 3. Fifty-two infants of similar ages whose entire milk requirements were furnished by ordinary pasteurized milk were also observed over the same period. Of these, 23 per cent developed x-ray evidence of "moderate" or "marked rickets," and 25 per cent developed x-ray evidence of "mild rickets."
- 4. In the infants receiving irradiated evaporated milk in whom x-ray evidence of "mild rickets" was found, there was always evidence of healing as shown by lime salt deposition. On the other hand, in the infants receiving ordinary evaporated milk and ordinary pasteurized milk, in many of the infants with mild rickets there was no evidence of healing.

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# INCIDENCE OF COMMON CONTAGIOUS DISEASES WITHOUT QUARANTINE IN THE PEDIATRIC SERVICE OF FIFTH AVENUE HOSPITAL

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THE Health Department of New York City groups the contagious diseases in two categories. Measles, scarlet fever, and diphtheria are called "major contagious diseases," and, if any of these occur, the quarantine is obligatory throughout the total length of incubation time of the last case. Chickenpox, whooping cough, German measles, and mumps are designated as "minor contagious diseases" by the Department of Health, and quarantine for these diseases is optional.

Prior to 1931, the children's service of Fifth Avenue Hospital lost yearly one-fourth to one-half of its admission days because the service was in quarantine on account of common contagious diseases. Most of the quarantine periods, however, were due to minor contagious diseases and were optionally enforced by the hospital authorities, who thought that by rigid quarantine rules they would have a better chance to suppress the spread.

In order to find if other hospitals, for the sake of safety, likewise preferred to quarantine their wards for the minor contagious diseases, circular letters were written in 1931 to several of the leading children's services of New York City. We found that the majority of private hospitals and many of the city hospitals preferred to quarantine for the minor contagious diseases and that many of them refused admissions for several months out of the year on account of quarantine. On the other hand, about 10 per cent of the children's services of New York City installed single rooms or cubicles for the isolation of the individual patients and did not quarantine the entire department. In these services, even when quarantine rules were enforced, only the single room or cubicle was quarantined and not the entire floor.

It is interesting that even in 1935 there was a considerable number of hospitals and institutions which voluntarily adhered in the most rigid way to the rules of quarantine for practically all the common contagious diseases of childhood. Strangely enough, the quarantine of patients to be discharged is more seriously enforced than is the quarantine of the

This study was made possible by the kind cooperation of the trustees of Fifth Avenue Hospital, the superintendent, Dr. W. E. Woodbury, and by the helpful assistance of the pediatric resident, Dr. J. V. Sullivan, and the nurse in charge of our service, Miss Grace Matthews. For part of this study, Dr. Gustav Nemhauser and Dr. Oscar Rimson assisted us.

newly admitted patients. However, as Straube pointed out in the Zeitschrift für Kinderheilkunde in 1928, a twenty-one-day isolation and quarantine for all new admissions is more important. In the Berlin city hospital for children it was found that in 1,256 admissions 110 cases of acute contagious disease developed at the rate of 8.7 per cent. Of the 8.7 per cent, 4.8 per cent were brought in from outside and only the 3.9 per cent occurring within the hospital could be considered as true cross-infections. Straube used group isolation technic and a twenty-one-day quarantine period in the admission ward. Only whooping cough was an exception, because the twenty-one-day isolation after admission was not sufficiently long. He also claimed that the group isolation and the group quarantine were not sufficiently effective and therefore advised individual isolation of the newly admitted patients in single rooms for at least twenty-one days in order to decrease the 3.9 per cent cross-infection rate.

Those who work in general pediatric services realize that unless the hospital is built so that not the ward, but the cubicle or the single room, is the unit, individual isolation on admission is impossible. The twenty-one-day admission quarantine would mean that almost every patient would remain for practically his entire stay in the hospital in the isolation ward because in an active pediatric service only the minority of patients remain in the hospital longer than this period.

After we found that not only Fifth Avenue Hospital authorities, but those of several other hospitals, believed that quarantine is an important weapon in the prevention of cross-infections in hospital wards for children, we tried to determine whether the benefit obtained from rigid quarantining is commensurate with the inconvenience it causes. Obviously, this question could be decided only by studying the cross-infection rate in a pediatric service which enforced no quarantine and comparing the results obtained—preferably on the same service—when rigid quarantine was maintained. Strangely enough, we found very little written about the quarantine problem in general pediatric hospitals. We found more literature on the bed isolation technic in special infectious disease hospitals not employing quarantine. Although we realized that the omission of quarantine and the treatment of several contagious diseases in the same ward are attended by more risk than the simple omission of the quarantine in general hospitals for children, we thought it worth while to review the results obtained in contagious disease hospitals using the bed isolation technic without quarantine.

In 1890 Grancher in France and in 1908 Biernacki in England described the treatment of several types of contagious diseases in the same ward by using the bed isolation technic—which we now term "aseptic technic." Admissions and discharges were uninterrupted; no quarantine was applied. Biernacki treated over 300 cases with this method and had

only 1.8 per cent cross-infections. Several other contagious disease hospitals in England, Scotland, and Wales followed his example. The most outstanding of these experiments were made by Caiger, Rundle, MacIntyre, and Thomson. These four men together with Biernacki reported upon 3,377 eases of contagious diseases in common wards. Their average cross-infection rate was 1.4 per cent; in some of the hospitals the admission of chickenpox and measles cases in the common wards was avoided as much as possible because of the recognized difficulty in preventing crossinfections when children with these diseases are treated in the same wards with those suffering from other contagious diseases. The Vienna Kinderklinik was the most famous place on the Continent where bed isolation technic was used and different contagious diseases were treated in the same wards. It was organized by Escherich and later continued by Pirquet. In 1913 this department reported 7 per cent cross-infections, a figure considerably higher than the cross-infection rate in the hospitals of the English investigators; but one has to remember that in Vienna all the patients were children, whereas in the English hospitals the departments for contagious diseases accepted both adults and children. Thus the Vienna Kinderklinik had a ward population more susceptible to contagious diseases, a fact which might explain the higher cross-infection rate. Measles and chickenpox cases were admitted in Vienna, whereas in some of the English hospitals efforts were made to eliminate the admission of eases of measles and chickenpox. As these two diseases were responsible for the majority of the cross-infections in Vienna, it is easy to understand why the English authors reported a lower cross-infection rate than Pirquet.

We investigated the frequency of cross-infections in some of the contagious disease hospitals of the United States. Information was collected partly from the literature and partly by writing circular letters to a number of contagious disease hospitals. It was found that in the Providence City Hospital (for contagious diseases), when necessary, different infections were treated in the same wards with aseptic bed isolation technic; the cross-infection rate between the years of 1910 and 1930 was as low as 1.9 per cent. In the contagious disease department of the Los Angeles General Hospital between 1928 and 1933, the patients were also treated with aseptic bed isolation technic in mixed wards when necessary. Cross-infection rate was only 0.44 per cent. Neither of these two hospitals adhered to quarantine rules.

In the Willard Parker Hospital of New York City, where each contagious disease is treated in a separate ward and a partial aseptic technic is used, the cross-infection rate varied between 0.8 and 4.0 per cent between the years 1929 to 1933.

In Brooklyn in the Kingston Avenue Hospital (for contagious diseases) the ward is the unit and not the cubicle or the bed. No aseptie

technic is used; quarantine rules are rigidly followed. During the years of 1930, 1931, and 1932, 0.6 per cent of all the patients admitted acquired contagious disease through cross-infection while in the hospital.

Encouraged by the low cross-infection rate of some of these contagious disease hospitals without quarantine, we concluded that we would not take a great risk if we studied the frequency of cross-infection in a pediatric service of a general hospital without the use of either quarantine or an aseptic technic. The Health Commissioner of New York City agreed to the experiment, and the authorities of the Fifth Avenue Hospital permitted us to conduct our investigation in their children's service.

Our purpose was twofold. We wished to find out whether the quarantine system is essential in the prevention of cross-infections in the pediatric service, and we wished to try out specific convalescent serums for the prevention of the common contagious diseases of children.

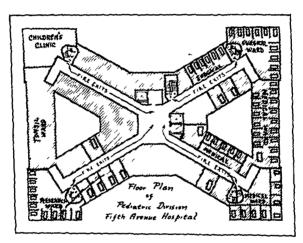


Fig. 1.

Our experiment was carried out on the entire children's service of Fifth Avenue Hospital from June 11, 1931, to July 1, 1934. During this period, 1,717 children were admitted to the children's service. The pediatric department, which occupies the whole second floor of the building, contains 63 beds (Fig. 1). Of these 63 beds, 9 are in separate rooms, 19 are in cubiculized wards, and 35 are in open wards. Even in the open wards the beds are 6½ feet apart and separated by glass partitions 8 feet high. Neither the partitions nor the cubicles reach the ceiling but stop 3¼ feet below it. The whole floor is divided into four equal units: two for the medical service, one for the surgical service, and one for the out-patient department. As the same doctors and nurses are in direct communication with all units, and the four wings of the floor are connected with corridors, for the purposes of this study we considered the whole floor, with the exception of the out-patient depart-

ment, as one unit. We excluded the out-patient department because the patients there had too short a contact with the nurses and doctors and no contact at all with the ward patients. Many of the children of the wards had quite intimate association with each other on the open terraces where those who were not too sick had the advantage of the open air.

Our scheme for the present study was as follows: When a case of contagious disease was diagnosed in the wards, the patient was reported to the Department of Health at once. An official diagnostician checked the diagnosis, and, if he agreed, the child was removed to a contagious disease hospital, or, if the parents objected, to his home. We did not quar-

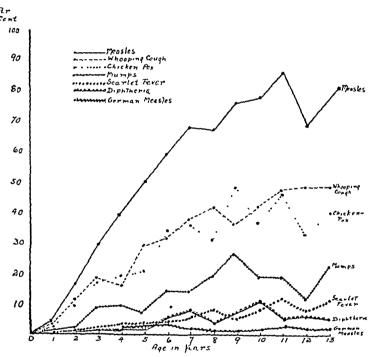


Fig. 2.—Frequency of contagious diseases in the past histories of 1.576 children admitted to the pediatric service of Fifth Avenue Hospital.

antine the hospital but kept on admitting new cases without interruption.  $\Lambda$  very eareful history with regard to contagious disease was taken of every patient and Dick and Schick tests were performed.

All patients who were discharged within the incubation period of a contagious disease on the ward were checked subsequently to find whether or not they developed the disease in question at home. If they did, the case was charged against the cross-infection rate of the ward.

Where a case of contagious disease occurred on the ward, the children were grouped in three categories: (1) patients who in the past had had the particular contagious disease. In case of searlet fever, patients with

negative Dick tests, and in diphtheria, patients with negative Schick tests were also put in this first group. Infants less than six months of age were considered as probably immune and were also placed in Group 1. Half of the group of susceptible children remaining were immunized against the specific disease by from 5 to 15 c.c. of convalescent scrum given intramuscularly, and they constituted Group 2. If a case of diphtheria had occurred, diphtheria antitoxin would have been given, but there was not a single case of diphtheria during our three years' study. The remaining half was not immunized and was kept as the control, or Group 3. All three groups were closely watched for the development of the contagious disease in question.

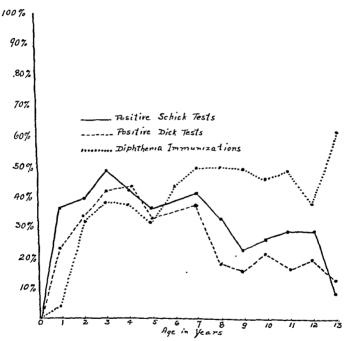


Fig. 3.—Frequency of positive Schick tests, positive Dick tests and diphtheria immunization histories among 1,576 children admitted to the children's service of Fifth Avenue Hospital.

We were very careful to select for the control and the treatment groups alternate children who were not immune. We considered the distance of exposure an important factor in our alternation. No aseptic technic was used; doctors and nurses carried out only the hygienic routine of general hospitals.

Figure 2 shows the curve of immunity of patients of different ages to the various contagious diseases as judged by a positive past history. The figures on which these curves are based were compiled from our own material collected during three years from 1,576 hospital admissions. We did not use all 1,717 admissions for obtaining these figures, as in

only 1.576 was the contagious disease history complete. From Fig. 2 we can see that the frequency of common contagious diseases is as follows: (1) measles, (2) whooping cough. (3) chickenpox, (4) mumps, (5) scarlet fever. (6) diphtheria, and (7) German measles. As a fair proportion of the hospital population was immune to measles, whooping cough, and chickenpox, and only a small proportion to mumps, scarlet fever, diphtheria, and German measles, it would have been erroneous to include these cases in the study of the value of convalescent serum or of quarantine.

Figure 3 shows not only the frequency of positive Dick and Schick reactions, but also the proportion of the children who had received diphtheria immunization in the past according to the history. It is worthy of note that 29 per cent of the children were immune to diphtheria without having been artificially immunized. This latter group of children probably became naturally immune through subclinical disease or through contact with diphtheria carriers. In the first year of life immunity transferred from the mother must also be considered.

TABLE I

CROSS INFECTION RATE IN 1,717 ADMISSIONS TO THE CHILDREN'S SERVICE OF THE FIFTH AVENUE HOSPITAL

TYPE OF CASE	TOTAL NUMBER	NUMBER CROSS INFECTED	PERCENTAGE CROSS-INFECTED
Susceptible, without prophylac-	409	23	5.6
Susceptible, with convalescent serum immunization	393	14	3.5
All admissions	1,717	37	2.1

During the course of our three-year study only 29 children among the 1,717 admitted developed contagious diseases. Of these 29 primary cases only 6 were followed by secondary infections. The secondary infections included 30 cases of measles, 6 of chickenpox, and 1 of mumps. The total of cross-infected cases, therefore, was 37, or 2.1 per cent, of the total admissions This cross-infection rate is between the 7 per cent cross-infection rate of the department for contagious diseases of the Vienna Kinderklinik where aseptic technic but no quarantine is used, and the low 0.6 per cent rate of the Kingston Avenue Hospital where rigid quarantine rules are observed without strict aseptic technic. fact that the cross-infection rate of the children's service of Fifth Avenuc Hospital prior to the onset of the omission of quarantine was 1.0 per cent for 1929 and 2.2 per cent for 1930 means that the omission of the quarantine system did not appreciably increase the frequency of cross-infections. We cannot explain the low figure of 2.1 per cent for cross-infections entirely by the use of convalescent serum for prophylaxis, since in the ease of German measles, searlet fever, and whooping

cough no secondary case developed either in the immunized or in the nonimmunized groups; not a case of diphtheria occurred during our whole three-year study period; and more cases of chickenpox developed among the treated cases than among the controls. However, in the case of measles and mumps our figures seem to indicate that the use of convalescent serum prevented somewhat the spread of the disease. added up the number of all the susceptible children who were on our wards when there was a chance for them to be secondarily infected, we find that out of 802 susceptible children, only 37 cross-infections occurred, making the cross-infection rate 4.6 per cent for the susceptible patients. If we eliminate all the susceptible children who received convalescent serum, the cross-infection rate rises to 5.6 per cent. From Fig. 2 we can see clearly that it is practically impossible that the composition of a ward population should be such that all the children at one time should be susceptible to a specific disease. During our three-year study, of 1,717 admissions only 802, or 47 per cent, were susceptible to the different contagious diseases to which they happened to be exposed. If the 37 cases of contagious diseases had involved the closing up of our wards for the usual length of time for quarantine, the hospital would have been closed for 452 days, out of the total of 1,124 admission days, or 40 per cent of the total time.

Table II gives the detailed consequences of the different primary contagious disease cases which occurred during our study in the children's service of Fifth Avenue Hospital.

After the analysis of the case histories of the patients who became cross-infected while in the hospital, we came to the conclusion that very few of them would have escaped infection even if we adhered to the quarantine system since most of them were on the wards at the time when the first case occurred. Therefore, it is obvious that we could have gained but little by carrying out the customary quarantine rules. On the other hand, by omitting the quarantine system we gained the following:

- 1. The hospital was of service to the sick children seeking admission for 452 more days in the course of three years than it would have been if the quarantine system had been maintained.
- 2. The internes and nurses had the opportunity to see nearly twice the number of cases that they could have if admissions had been avoided during 40 per cent of the time.
- 3. Each month of quarantine means a loss of from \$400 to \$500 to the hospital because of the necessity of maintaining the same staff of doctors, nurses, and attendants without being able to accommodate private patients. This loss in the course of 452 days of quarantine would have amounted to from \$6,000 to \$7,000.

Table II

Contagious Diseases Occurring in the Pediatric Service of Fifth Avenue Hospital From June 11, 1931, to July 1, 1934

			IMMI	NIZED	CON	TROL	<del></del>
				SES		SES	}
NO.	DATE	DISEASE	mom a r	CROSS-	FOTAT	CROSS-	LENGTH OF
			TOTAL NO.	IN- FECTED	TOTAL NO.	IN- FECTED	EXPOSURE
	0.000.001	7.1.11	3	FECIED	4	FECIED	
1 2	6/26/31 2/15/32	Rubella Rubella	19	_	22	_	11% days 2 days
	Total	Rubella	22		26		
3	12/31/31	Scarlatina	<u>-</u> -		3		71/ 30-0
4	3/23/32	Scarlatina Scarlatina	16	_	10	-	14 days 2 days
5	4/25/32	Scarlatina	6	-	7		2 days
6	7/13/32	Scarlatina	2 9		9		6 hr.
	5/16/34	Scarlatina	! <u>-</u>		8		2 hr. 1 day
	Total	Scarlatina	38		37		
8 9	6/19/31	Pertussis	3	-	3 3	-	2 hr. 8 days
10	7/ 2/31 9/ 1/31	Pertussis Pertussis	9	_	3	_	1½ days
îĭ	10/ 8/31	Pertussis	1	-	4	-	1-21 days 1 day
12	10/30/31	Pertussis	13	_ '	4	- 1	2 days
13	8/11/33	Pertussis	19	-	14	{ -	26 hr.
14	9/ 2/33	Pertussis	12	-	12	-	2-7 days
15 16	10/23/33	Pertussis	12 11	] -	14 16	-	6 hr. 7 days
17	12/12/33	Pertussis Pertussis	10		17	-	1-8 days 4 hr. 16 days
	Total	Pertussis	96		90		4 m. 10 days
18	5/30/32	Parotitis	6		6		
19	6/ 8/32	Parotitis	16	_	20		9 days
20	4/14/33	Parotitis	26	-	31	] _ }	3 days 29 hr.
21	4/20/34	Parotitis	17	-	36	1 1	4 hr. 4 days
						2.8%	
	Total	Parotitis	65		93	1	
22	5/17/32	Varicella	14			1.7%	
23	3/ 4/33	Varicella Varicella	14	5	18	$\tilde{1}$	6-8 hr. 12 hr38 hr.
			33	15.0%	62	1.5%	12 nr35 nr.
	Total	Varicella	47	5	80	1	<del></del>
	·		l	10.6%		1.2%	
24	7/17/31	Morbilli	4	-	4	-	1 day
25	3/21/32	Morbilli	34	20~	44	15	20 hr. 2 days
26	1/18/33	Morbilli	16	5.0%	26	34.0%	C 1 C1/ James
07	0 (10 (00	35 1 33	Ì	_		11.0%	6 hr61/2 days
27	2/13/03	Morbilli	23	5 22.0%	6	5	6 hr. 111/2
28	3/25/33	Morbilli	22	1	2	33.0%	days 1-16½ days
29	5/ 6/33	Morbilli	000	4.0%		50.0%	1-10-72 (11)5
-2	07 0733	Moroini	26	4.0%	1	-	1-20 days
	Total	Morbilli	125	9		21	
	<u> </u>	1 ,	1	7.0%		25.0%	
	All cases	j	393	14	409	23	
				3.5%		5.6%	
		Total	S02 c	oss-infect	ed 37 c	ur 4.6%	

#### CONCLUSIONS

- 1. For the past three years in the children's service of Fifth Avenue Hospital quarantine was not observed.
- 2. In the place of quarantine and the asentic technic, specific convalescent serum was used for prophylaxis against all common contagious diseases in half of the susceptible groups. One-half of the susceptible children were used as controls.
- 3. No secondary cases of German measles, whooping cough, or scarlet fever occurred.
  - 4. The chickenpox convalescent serum appeared to be of no value.
- 5. Serum from convalescent patients with mumps apparently decreased the morbidity of parotitis from 2.8 per cent to 0; measles convalescent serum apparently decreased the incidence of cross-infection of measles from 25 per cent to 7 per cent.
- 6. The order of frequency of cross-infections was measles, chickenpox. and mumps.
- 7. Of 1.717 hospital admissions 37, or 2.1 per cent, became infected while in the hospital.
- 8. Only 47 per cent of the ward population were susceptible to the contagious disease to which they were exposed.
  - 9. The cross-infection rate of the susceptibles was 4.6 per cent.
- 10. The lack of quarantine and the lack of aseptic technic did not anpreciably increase the cross-infection rate of our pediatric service.
- 11. The disadvantages of quarantine for a general pediatric service are much greater than the good achieved by its use.

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1225 PARK AVENUE

### GROWTH OF THIRTY-TWO EXTERNAL DIMENSIONS DURING THE FIRST YEAR OF LIFE

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DATA in the literature on the external dimensions during the first year of life are meager.1-3 In this paper means and standard deviations\* for thirty-two external dimensions are recorded by certain subdivisions of age under one year (Table I, A and B). Similar data for the dimensions of the thoraco-abdominal cavity, the cardiac silhouette, the mediastinum, the radius and ulna are recorded elsewhere.4,5

Means for dimensions at age intervals not given in the table may be readily obtained by constructing curves from the mean values and interpolating.

The infants used in this study were born in the Fifth Avenue Hospital and were supervised from birth in a special clinic. They came from homes of moderate income. The number of infants classified by sex and racial origin and the number of times they were measured is shown in Table II. The instruments used and the dimensions measured have been described elsewhere.7

#### THE BODY PROPORTIONS

Since the external dimensions of the body grow at different rates during the first year of life, there results a change in the body proportions. In relation to total body length all external dimensions in Table I become smaller during the first year of life with the following exceptions: The biacromial diameter of the trunk, the length of span, and the foot dimensions remain relatively unchanged The bicristal diameter of the trunk and the length of the humerus, femur, and tibia become relatively larger. Weight also increases more rapidly than total body length. The most striking change in the body proportions is in the relative size of the head, the head circumference—total body length index falling from 68.3 at birth to 60.8 at one year.

A number of changes occur in facial configuration. The face at birth is broad, particularly in its lower portion, the nose is broad and short

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\*The standard deviation is a measure of the dispersion of values around the mean one standard deviation on each side of the mean includes 67 per cent of the cases, and two standard deviations 95 per cent of the cases. In older anthropometric studies the percentile method has been used for expressing variability. More recently, however, it has been replaced by the standard deviation. Though more laborious to calculate, the standard deviation has a number of the percentile method. It is, in general, less affer algebraic properties it is more usef algebraic and normal groups. It is also more useful in cases of discontinuous variation. Furthermore, the percentile is not infrequently indeterminate

THE EXFERNAL DIMENSIONS OF MALES BY CENTAIN SUBDIVISIONS OF AGE UNDER ONE YEAR (IN MILLINETERS) TABLE I A

						نج			AGE IN WEEKS	VEEKS						
	0.3	25	4.7		8-15	ž.	16-23	23	21-31	11	32-39	39	10.17	1.7	18-55	
	MEAN	ST. D.*	NEAN	ST. D.	MEAN	ST. D.	MEAN	Sr. D.	MEAN	ST. D.	MEAN	ST. D.	MUNN	ST. D.	MEAN	Sr. n.
Total body length	518.50	17.00	552.56	23.60	600.83	27.21	651.07	21.73	685.11	22.53	717.73	25.77	745.89	29.72	765.68	22.70
Length of span	511.90	21.10	517.56	26.60	591.64	25.30	635.52		675.17	28.60	706.63	31.20	736,51	31.90	758.14	30.00
Body weight (gm.)	3515.10	570.00	-	658.00	5750.00	720.00	7090.00	-	8207.20	1000.00	9291.00	1052.00	10,060.00	1181.00	10,800.00	1210,00
Sitting height	350.53	15.60	370.60	19.10	399.10	20.00	431.23	20.00	150.51	19.10	469.30	23.30	479.05	19.70	490.06	21.50
Circumference of 353.52	353.52	11.65	377.16	13.20	399.30	13.35	417.87	12.00	436.12	11.90	418.01	13.95	458.89	12.05	464.88	13.10
head													1	1	1	1
Cephalie length	120.70		128.40	6,14	132.60	7.28	137.90	5.68	143.90	06.4	117.20	6.05	151.97	2.2	155.30	7.20
Cephalic breadth	95,00	1.70	102.13	1.60	109.28	6.30	117.24	1.62	119.37	7.14	123,48	6.18	125.79	5.38	129.08	5.33
Dinmeter of face	73.15	-	77.59	17.	85.38	4.68	90.33	4.56	92.93	4.89	95.33	5.29	95.10	66	96.77	5.33
(himalar)																
Dumeter of face	58.08	3,62	(12.88	3.63	67.28	4.00	79.17	3.57	72.81	3.76	73.91	3.96	74.97	0u.t	75.14	3.75
(bigonial)																
Upper facial length	33.25	2.13	36.21	ei ei	38.34	61	10.33	2.16	11.85	2,31	42,53	2.52	43.13	2.31	43.65	2.71
(masion-pros-		-								•						
thion)										-						
Height of lower	17.50	1.57	19.15	1.62	20.77	1.53	21.94	1.65	22.90	1.92	23,81	1.74	24.42	2.20	25.56	2.38
Jaw														_		
Height of nose	22.83		24.81	1.78	26.14	2.26	28.00	1.64	29.09	2.40	29,59	1.82	30.36	1.99	30.01	1.90
Breadth of nose		1.75	23,58	1.67	24.47	1.67	25.43	1.62	25.89	1.65	26,32	1.06	26.95	1.51	27.27	1,31
Inter-inner cantlins			23.14	1.18	21.03	1.66	25.09	1.59	23.77	1.82	26.20	1.79	26.42	1.81	26.61	1.01
diameter										_						
Length of palpe-	21.26	1.91	22.31	1.67	23.56	1.17	24.88	1.53	25.70	1.71	26,53	1.72	27.00	1.59	27.63	1.68
bral fissure		_		_						_						

\*St. D. means standard deviation.

Table I A-Cont'd

,	1		1	<u></u>	_			1	3	0	တ	53	وِ	S	<u></u>	io		13	≘.	9		č1	œ.	<u>[3]</u>	
	اجر	ST. D.		<u>ښ</u>	C i	16,51		t	20.7	7.60	6.9	5,1	1.0	ci	C.	e i		12.25	<u>.</u>	18.5		3.75	ıς	ci	
	18-55	MEAN		18,15	31.39	167.59		9	179.80	121.04	134.32	103.88	92.20	53.21	11.73	16.47		192.37	132.86	363.00		36.77	116.10	16.10	
		2 11/2		37	50.0	21.10		!	<u>.</u>	7.01	7.68	5,67	3.97	5.3	6	c	i i	10.62	7.69	16.67		1:31	6.03	2.71	
	10-11					1,52.06			175.30	119.50	199.26	99.71	88.73	51.01	13.31	10,15		183.01	127.08	316.81		31.79	110.61	87	
		4	21:17:	3.04	0	21.53	_		9.40	6.31	7.39	0.90	0.	3.60	000	0	i	11.05	8.00	17.71		3.66	5.78	2.8	
	08-33		MLAN	17.80	20.00	11.11			169.10	117 51	10101	95.78	21 98	101	20.00	2 2	9 191	177.86	122,15	335.73		31.75	102.01	13.11	
S			ST. D.	:-	_	1 6	_		9.11	7.77	20.0	15	19.6	0.0	100	; c	Tot	10.87	6.73	16.03		90.0	18.7	2.56	
IN WILKS			MEAN	00 21	0000	193.16			161.00	110 01	117.04	11.1.0	00.00	110	21.0	57.07	3	167,19	113.36	311.61		39.86	101.23	11.38	
NI CLOY	Ι.	İ	ST. D.	5	) ;	17.51	3		8.96	9	0.10	1 6	0 1	00.0	100	200	3.7	98 0	06.9	11.70		3 0.8	2.7	5.17	
	16.93			١.		00.00			151.90	,	100.35	00.00	30.00	00.07	10.27	10.00	33.30	151.00	107 58	903.15	27.0/3	21 67	05.66	39.79	
	,		ST. D.	1	99:1	850	00'61		9.18	1	2.58	6.75	7.0	200		2000	27	0	200	10	07.01	3.10	200	66	
	110	01.0	MEAN		13.22	27.17	650.93		111.10		98.93	102.14	80.90	73.92	12.55	37.00	37.57	0	00.00	070.10	2	00	00.00	37.02	
			CT. D.		ci 21	1.95	19.90		9.00		6.16	5.7	11:	3.36	 	1.85	1.90	t	0 12	000	Lin	I.	- 0	2 6	
		1	Minn	NI I''	10.37	26.74	350,59		130.30		90.18	93.1	73.60	69.3 \$	39.92	35.20	35,60	6	130,30	91,24	76,00	0	00.00	31.75	
			*	SI. D.	3.00	1.77	19.17		8, 17		6.65	5.90	1.1	3.62	2.31	2.28	2.03	;	2,7	0.50	0.::1		21 0	100	1
		: -	١.	NVII	37.09		323.84		119.57			85.38						1	20.12	09778	252.10	•	21.98	31.01	1) (1)
			f		Tomath of our	Brendth of enr	Circumference of	thorax at tho	nipples Receioniel diem:	eter	Bieristal diameter	Length of humerus	Length of radius	Length of hand	Length of palm	Breadth of palm	Length of middle	finger	Length of thigh	Longth of tibin	Length of lower	extromity	Tongil of for	Breadth of foot	2007 70 111101

Table I B

Franty by Certain Subdivisions of Age Undy One Year (in Mulliweless)		32.30 10.17 15.50	D. MFAN ST. D. MYAN ST. D. MEAN ST. D.	697.68 19.26 733.38 25.26 717.67	22,10 711,28 27,30 710,17	8160.00 821.00 9200.00 1068.00 9900.00 10	152.08 16.30 165.69 21.00 177.33	151.58	5.11 117.12 5.67	122.71 1.72 121.91 4.91 126.60	91.50		3.16 71.10 3.56 72.64 3.66 73.17 5.06	103 1003 900 1151 0.19 41.08 9.15	1000	1.26 22.92 1.93 23.02 1.87 23.73 2.04	28,36 2,13 28,92 1,77 30,27	25,59 1.44 26.17 1.87 26.77	25.32 1.68 26.00 2.18 26.07		1.68 26.09 1.28 26.39 1.77 27.00 1.47
s or Age Un	AGE IN WEFES	-	MEIN ST. D.	671.38	657.37	7670.00	136.97	423.96	139.10	118.64	90.10		1.01 70.27 3	20 70		21.82	27.40	24.90	54.76		25.02
N Stybbivision	AGE	16-23	MEAN ST. D.	632.11 23.66	618.31	110.00 7	115.57 20.90			113.58	87.30 5.10		68.16	9890 010	O Proper	21.06	26.36 1.97	24.26	21.24		24.07 1.63
CERTAIN		12	ST.D.	0 23.08	5 24.00	10 720.00/6	2 17.80				89.4 97		5 3,56	0 23			0.5.06				6 1.84
ALT'S BY		x	MEAN	5 589.00		0 5310.00	0 389.12						8 65.75		00.00		3 25.00		1 23.38		2 23.26
or Fru		2-	ST. D.	18 20.95		00.570.00	17.60		. ~~		11 1.56		3.78		1.33		8 1.73				1.72
RYAL DIMENSIONS OF		_	VIEVN	511.98								_	9 60.60				23.18				21.99
, Dine:		= ::	31. 2.	19.51							•		90'\$ 8		76.4		1.80				1.91
TFRNA		=	11.15	1,2	. 17		•	٠.	117.81		71.33		57.38	20.00	50.50	17,30	22.01	21.87	21.15		20.96
The Extr	A CONTRACTOR OF THE PROPERTY O			Total body length	Length of span	Body weight (gm.)	Suting height	Creamference of head	Centalic length	Coppale breadth	Diameter of face	(Dimalar)	Diameter of face	(bigonial)	(nusion-prosthion)	Height of lower jaw	Height of nose	Breadth of nose	Inter-inner canthus di-	ameter	Length of palpebral fisance

TABLE I B-CONT'D

			•••		-	., -																
\ 	3	sr. n.	19:0	191		01.61	8.26	6,50	6.20	10.1	4.03	57.55	90.6	i c	i	10.48	8.16	15.15		e: ::3	08 +	10
		MEIN	17.67	200		66.711	173.29	117.89	130,05	99.65	88.51	51.31	15 61		11:00	187.96	129.83	353.61		3.55	111.60	12 82
	12	ST. D.	08.0	ic	1	) 	9.03	6, 10	6.53	5.06	3.83	0 30	001	1		9.70	7.60	11.90		3.56	15.15	2.50
	10-12	MEAN	16 16	00.00	100	137, 18	168.65	111.83	191.53	96.36	11.5	20 01			13,11	181,01	121,26	310,31		34,04	106,53	15.99
	S.	ST. D.	60 0	1	50°	18.55	9.13	6.88	1.90	or.	3.01	0	10			08.6	7.50	15.80		1.18	1.80	2.53
	32-38	MEAN		10.01	120.33	128.38	161.79	111 60	101 09	21.00	5000	200	10.00	10,00	13,03	175.53	118.17	327.91		32.91	102.86	11.66
	11	ST. D.	6	6.1	9	19.55	08.8	9 1 9	101	27.6	1 00	5 6	i e	8	10.5	9.19	6.58	13 52		51.33	3,98	2.95
I WIITKS	15-47	MEAN	!!	1.5.1.5	58.69	107.13	35.05	106 90	13 11	20.00	9 00 00	50.0	00.00	38.03	10.33	167.56	113.30	313.08		31.15	97.39	39.63
AGE: IN	=	ST. D.	1	2:	 6:	17.65	0 16		900	90.0	200	2 5	2 2		6.1 6.1	0.76	1	11.11		3.14	16:1	2.33
	6.91	MULLIN		53.56	5.75	390.05	00 00	101.69	60.101	92 60	00.00	(0.00)	13,16	36.73	37.97	163.91	10.501	901 03		29,55	91.99	37.33
	12	S.F. D.		2.5	e:0	19.85	000	0 10	100	00.0	000	0,30	_   :i	1.8.1	1.91	0 11	7.00	10		.1.18	25.1	2.19
	8-15	71.15		61:13	36.34	368.09	-	00.05.	0.1.4.5.	03.50	20.00	71.15	40.75	31.86	36.03	1 (0 03	07.09	20 000	00'00	18.96	86.58	34.88
		6	:	19:5	01.0	17.45	t	00.	2 1	5.61	00.1	3.51	1.93	12	2.16	10	10.5	2 5	00.61	3.38	90 1	ei ei
	1	-   2	N. C. S.	38.66	57.17	342.11	,	125.72	81.15	89.89	73.17	67.21	38.68	33, 17	34.61	00 00 5	00'00'	20.00	2 10,30	00 20	90.00	32.99
		ا ا				19,10		Si S	5.36	5.6	30.5	د: د:	2.11	1.89	1.01	6	0000	5.0	02:17	3.00	06.0	61
		-	MEIN	26 19		318,65		116.50	22.72	81.60	70.91	61.63	36.62	31.57	33.79		20:121	200.00	730°T	01.76	000	29.88
				41. 0.0 0.00	Length of cau	Breadth of car	nav at the nipples	Binerominl dinmeter	Bieristal diameter	Length of humerus	Length of indius	Length of hand	Length of palm	Brendth of pulm	Length of middle fin-	rer.	Length of thigh	11011	trength of lower ex-	Traight of foot	Longth of foot	Breadth of foot

and the bridge depressed. The palpebral length and particularly the inter-inner canthus diameters are large. At one year the face is relatively narrower, the nose longer and narrower and the eyes smaller and closer together.

The lower extremities grow more rapidly in length than the remainder of the body. This is true also of the bicristal diameter and confirms the observation that the lower portion of the body grows more rapidly than the upper portion during this age period.

#### SEX

At birth the male infant is larger in the external dimensions than is the female infant, indicating a more rapid growth during prenatal life. The female infant, on the other hand, is more advanced physiologically as indicated by the earlier ossification of the epiphyseal centers. Other differences during prenatal life are the larger number of male conceptions, estimated at about 108 males to 100 females, and the higher death rate among male infants. The higher mortality among males continues after birth and is found for every disease during infancy except pertussis and erysipelas. It is, therefore, of interest to determine whether any differences in growth exist during this age period.

Although boys are larger than girls at all age subdivisions no differences in body proportions were noted for the external dimensions measured. There was also no significant difference in the variability of the various dimensions.

TABLE II

DISTRIBUTION OF INPANTS MEASURED BY SEX AND NATIONALITY

NATIONALITY	NUME	er of in	FANTS	NUMBER OF TIMES MEASURED				
	TOTAL	M ILES	FEMALES	TOTAL	MALES	FEMALES		
All nationalities Mediterranean North European Central European Jewish U. S. A. Undetermined	198 38 65 21 44 14 16	94 16 32 12 22 6	104 22 33 9 22 8 10	1328 233 476 151 327 88 53	598 84 220 79 162 34 19	730 149 256 72 165 54 34		

## NATIONALITY

No consistent differences were found in the head dimensions or indices of infants from the national groups designated in Table II. There was also no difference in the bimalar diameter of the face. Other dimensions were not calculated since head shape is ordinarily considered one of the most striking of national characteristics.

## SUMMARY

- 1. Means and standard deviations for thirty-two external dimensions are recorded by certain subdivisions of age under one year.
- 2. Differences in body proportions at birth and at one year are described.

3. Neither sex nor nationality has any influence on body configuration during the first year of life.

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# THE COMPARATIVE VALUE OF THE SCHILLING DIFFEREN-TIAL BLOOD COUNT AND THE SEDIMENTATION OF THE ERYTHROCYTES IN ACUTE RHEUMATIC FEVER IN CHILDHOOD

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IN THE treatment of acute rheumatic fever it is of importance to know when the acute process has completely subsided and when to allow the patient out of bed. This is especially significant in those with first attacks in order to prevent, if possible, the development of serious cardiac lesions. The caution of various clinicians is well summarized by Lewis, "Convalescence should proceed slowly and be well consolidated. In cases of carditis the end of active infection is most difficult to gauge and months must pass before recovery can be regarded as complete."

Since the mere disappearance of symptoms can be no indication of recovery,<sup>2, 3</sup> various guides have been sought—subsidence of fever for an indefinite period of weeks, normal pulse rate, and total white cell count being the usual criteria. These, however, have been found normal in the presence of low grade infection and are therefore unreliable. Numerous observers have reported the value of the sedimentation of the red cells in indicating quiescence<sup>4,5</sup> and have emphasized the importance of keeping convalescent rheumatic fever patients at rest until this test is normal, the one important point in therapy.

Another blood examination, the Schilling differential count, wherein the presence of immature white cells is noted, has been much used as an index of active infection in various acute illnesses, and its value has been repeatedly established. It was deemed useful, therefore, to compare the Schilling smear and the sedimentation of the red cells in cases of acute rheumatic fever, especially since these tests have not given corresponding results in other conditions, the sedimentation test appearing less sensitive than the Schilling count. In acute appendicitis, for example, it is interesting to note that the sedimentation rate is often normal in the presence of a marked left shift in the Schilling smear.

For this reason we applied these tests in a series of acute rheumatic fever cases. It was first planned to study primary cases without evident cardiac involvement, but such cases were too few, and it became necessary to include those with acute and chronic carditis. Even with these it was possible to collect but twenty-five suitable cases in three years. On this material our study is based,

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#### METHOD

For the sedimentation tests venous blood was withdrawn and mixed with 2 per cent sodium citrate solution in the proportion of one part of citrate to five parts of blood. This mixture was placed in tubes and allowed to stand at room temperature. Readings were made at appropriate intervals. Schilling smears, total white counts, red cell and hemoglobin determinations were also done on admission. The Schilling counts and the sedimentation tests were made at weekly or ten-day intervals until normal. Our patients were under observation from three to sixteen weeks.

There are many methods in use for determining the sedimentation of the red cells, each depending on some slight variation in bore or length of the tube used with altered markings. The principle involved is the same and these slight modifications only cause confusion and require a new set of normal values for each new tube. There is, however, one main difference in systems used. One system measures the sedimentation time; the other measures the sedimentation rate. We used the Linzenmeier and the Westergren methods as an example of each of these systems. In our later work we preferred the Cutler method in place of the Westergren and finally used it exclusively.

Sedimentation time is measured by the Linzenmeier method, in which a short tube 70 mm. long with a 5 mm. bore is used and graduated at 6, 12, 18, and 24 mm. The time necessary for the column of cells to fall to the 18 mm. mark is recorded—normally two or more hours. The disadvantage of the method is the necessity for constant watching of the tube.

Sedimentation rate is measured by the Westergren and Cutler methods. The Westergren tubes are 300 mm. long and graduated from 0 to 200 mm. in 1 mm. intervals. The distance the cells drop in one-half and one hour is noted—normally 10 mm. or less at the end of one hour.

The Cutler tube is also a short tube 70 mm. long with an internal bore of 5 mm. and is marked from 0 to 40 mm. The distance the column of cells falls in one-half hour is read and should be 10 mm. or less, normally. Some take a second reading after one hour, but there is very little additional drop.

TABLE I READINGS ON CONTROL CASES WITHOUT INFECTION, TO ESTABLISH NORMAL FIGURES FOR VARIOUS TESTS USED

====								
NORMAL	AGE	SCHILLING	SEDIM	ENTATION TI	ESTS		HG.	
CONTROL	IN	PER CENT	LINZEN-	WESTER-	1	R.B.C.	%	HG.
CASES	YR.	IMMATURES	MEIER	GREN	CUTLER		SAHLI	GM.
1	12	10	3.3 hr.	13.0 mm.		4,860,000		
2	12	8 5	12.0 hr.	2.5 mm.	[	4,770,000		
	11		5.0 hr.	10.0 mm.	1	4,690,000		
4	10	10	6.0 hr.	4.5 mm.	1	4,890,000		
ō	8	10	4.0 hr.	6.0 mm.	}	4,370,000		
4 5 6 7 8 9	11	3	6.0 hr.	5.0 mm.	}	4,610,000		
7	11	9	5.0 hr.	5.0 mm.	}	4,790,000		
8	7	9 8 5	4.0 hr.	5.0 mm,	1	4,500,000		
	10		3.5 hr.	7.0 mm.	,	5,200,000	92	
10	7	7	3.0 hr.	8.0 mm.	1	5,080,000		
11	7 8	9	1	1	7 mm.			10,5
12 13	10	9 7	{	{	4 mm.		83	12.1
14	110		}	}	5 mm.		96	14.0
15	12	9	}	}	3 mm.			12.1
16	7	9 7	1	}	6 mm.		88	12.3
17		3	1	į	4 mm.	3,180,000	76	11.0
îś	8	6	1	f	10 mm.	4,820,000	80	11.5
19	8 8 6	8	)	}	5 mm.	14.170.000	70	10.4
20	7	4	}	1	10 mm.	4,280,000	78	11.4
	<del></del>	<u> </u>	<i>.</i>	1	7 mm.	4,610,000	80	11.4
						-, -,-00.		TT.0

In our control series all three methods for determining the sedimentation of the red cells gave accepted normal values, but in the sick patients the Cutler and Linzenmeier readings often reached normal while the Westergren was still rapid.

Various factors, such as anemia, cell volume, room temperature, etc., have been shown to cause appreciable errors in the reading of the sedimentation test.<sup>11</sup> Kahlmeter,<sup>12</sup> Walter,<sup>13</sup> and others have used a corrected sedimentation rate index. Rourke and Ernstene<sup>14</sup> have found the normal limits of the corrected index to be from 0.08 to 0.35 mm. per minute, which could produce a marked distortion in delayed readings. However, the degree of anemia was not sufficiently marked in our cases to cause serious errors, and corrected readings were deemed unnecessary for all practical purposes.

Since Fahracus published his first observations on the sedimentation rate in 1918, there has appeared a vast literature on the factors controlling this phenomenon, and we need not review these theoretical studies here. They are well summarized by Walton.<sup>15</sup>

## ANALYSIS OF CASES

In our work it soon became apparent that the Schilling blood count and the sedimentation tests both reacted to the rheumatic infection in its early stages. There were usually an abnormal number of polymorphonuclear leucocytes of the immature form in the blood stream from one to several weeks after the temperature and pulse became normal. At times the blood smear appeared normal simultaneously with the fall in temperature or even anticipated this improvement, an observation which corroborated earlier work done in acute infections with the Schilling smear.<sup>9</sup>

With occasional exacerbations and reappearance of joint swellings, or with the onset of a pericarditis, an increase in the immature white cells and increased sedimentation time and rate invariably appeared (Case 7). With each subsidence of signs and symptoms, however, the sedimentation tests always lagged in their return to normal and remained rapid for weeks after the disappearance of immature cells from the blood. Thus the sedimentation tests must be considered more sensitive to the presence of active rheumatism than the Schilling smear (Table II).

This is perhaps best explained by the growing belief that some factor may play a rôle in rheumatism, which is slow in subsiding after the acute infection has actually ended. To this there would be no response of the hematopoietic organs and hence not reflected in the Schilling smear. In many cases of rheumatism an cosinophilia occurs<sup>16, 17</sup> during some stage of the illness. One of our patients showed an cosinophilia of 10 per cent, another of 15 per cent. This suggests the presence of an allergic factor, but the sedimentation rate is generally delayed in allergic conditions. In any event there is a factor at work during convalescence

from acute rheumatic infections, which could conceivably cause a physicochemical change in the blood affecting the sedimentation rate and time.

TABLE II

Illustrative cases showing how temperature and pulse first reach normal, to be followed shortly by the Schilling count and finally by the sedimentation rates. Abbreviations: TPN (temperature and pulse normal), N (normal). Normal values: Linzenmeier—120 minutes or more; Westergren—10 mm. in one hour; Schilling—about 10 per cent or less; Cutler—10 mm. or less.

Date	Aug., 1932 2	8_	15	22				
Case 6 Linzenmeier in minutes Westergren mm. in 1 hr.	T103 50 56	40 60	TPN 70 49	N 120 25				
Schilling per cent immatures	23	N 7	_ 9	11				
Date	Mar., 1932 24	Apr.	8	18	28	May 10	June 9	30
Case 7 Linzenmeier in minutes Westergren mm. in 1 hr. Schilling per cent immatures	T101 15 90 16	15 100 N 9	TPN 50 40	45 74 24	50 60 20	12 70 24	45 87 12	82 20
Date	Apr., 1933 15	21	29	May 5	13	20	26	
Case 10 Linzenmeier in minutes Westergren mm. in 1 hr.	T102 9 147	17 106	TPN 30 72	45 45	30 15	100 19	105 12 N	
Schilling per cent immatures	47	15	14	N 11	9	10	5	
Date	Mar., 1933 30	Apr.	10	16	24	May 1		
Case 8 Linzenmeier in minutes	T101 25	20	TPN 45	77	90	N 130		
Westergren mm. in 1 hr Schilling per cent immatures	22	85	48	28 N 11	20	N 10		
Date	Jan., 1935 19	28	Feb.	20	Mar. 8		<u> </u>	
Case 16 Cutler mm. in ½ hour Schilling per cent	T104 31	TPN 29 N	24	19	N 5			
immatures	30	11	7	<u> </u>		<u> </u>	]	

In order to obtain normal values for the laboratory tests we were to perform on our patients, we examined a series of twenty normal children, i.e., without acute infection as evidenced by a normal Schilling count with immature "stab" cells below 10 per cent. Red cell and hemoglobin determinations and sedimentation tests were done on these children. The Westergren and Linzenmeier methods were used in the first ten eases, the Cutler method in the last. The highest normal value for the Schilling count was 10 per cent. In the Linzenmeier tubes it

took from three to twelve hours for the column of cells to fall 18 mm. In the Westergren tubes the column fell from 2.5 to 13 mm. in one hour. The high figure in one case was accepted as normal in view of a normal blood smear, a normal Linzenmeier test, and a negative history (Case 1). The normal figures for the Cutler tube ranged from 3 to 10 mm. in one-half hour.

The following illustrative cases are described in some detail for the various points of interest they offer:

CASE 6.—J. B., male, aged ten years, was admitted Aug. 2, 1932, with painful swellings in the ankles, knees, and hips, and fever for fourteen days. There was no previous history of a similar nature. The positive physical findings were exquisitely tender and swollen ankles, and a short, soft, blowing, systolic murmur heard at the apex of the heart. The temperature was 103° F.

Both sedimentation tests were very rapid and the Schilling smear showed numerous immature cells. One week later all symptoms had disappeared, and the

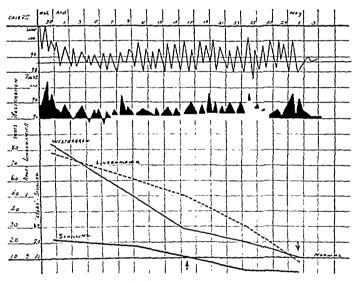


Chart 1.—Case 8. Note how the Schilling curve reaches normal two weeks before the sedimentation tests (arrows indicate normal).

temperature and pulse were normal. The smear was normal, but the sedimentation tests were still unchanged. They began to improve during the following week; the Linzenmeier reading became normal two weeks after the Schilling had become normal, and the Westergren reading was much improved but lagging (Table II).

Case 7.—M. G., male, aged eleven years, was admitted March 24, 1933, with pain and swelling in the shoulders and knees three days after the onset of a sore throat, the duration of the joint symptoms being one week. The temperature on admission was 101° F. There were swelling and redness of the knees. The heart was negative. The red cells were 2,700,000; the hemoglobin content was 78 per cent (Sahli) and the leucocytes, 6,500.

Both sedimentation tests were very rapid, the smear showing but a moderate left shift (16 per cent immature cells). All tests indicated the presence of active infection, however. The sedimentation tests continued very rapid though the smear

became normal one week after admission. During the second week in the hospital, however, immature cells reappeared in the blood, followed by an acute exacerbation of all symptoms with joint involvement and a temperature to 103° F. The heart remained negative. Both sedimentation tests were markedly increased, the column in the Linzenmeier tube falling 18 mm. in twelve minutes. One month after subsidence of this second attack, the immature cells had practically reached normal, while the sedimentation tests, though improved, remained high, only approaching normal three weeks later (Table II).

Case 8.—C. H., male, aged twelve years, admitted March 30, 1933, had a painful, tender swelling of the left ankle for three days. There was no previous history of rheumatism. There was a soft, blowing systolic murmur at the apex of the heart.

The laboratory findings were: R.B.C., 4,900,000; hemoglobin, 84 per cent (Sahli); and W.B.C., 18,400. The Linzenmeier tube showed a drop of 18 mm. in

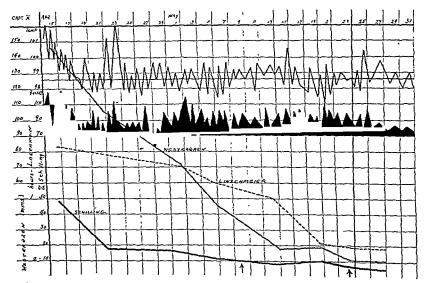


Chart 2.—Case 10. Note the extremely rapid Westergren and the prolonged Linzenmeier tests, which reach normal two weeks after the Schilling count (arrows indicate normal).

twenty-five minutes. There were 22 per cent immature cells in the blood. Ten days later all tests showed improvement with normal temperature and pulse, but activity was still indicated. Seventeen days after admission the smear was normal and the sedimentation tests improved. Both Linzenmeier and Westergren tests became normal two weeks after the blood smear, showing once again the greater sensitivity of the sedimentation tests. The child was not allowed up until all readings were normal (Table II) (Chart 1).

Case 10.—C. F., female, aged nine years, was admitted April 15, 1933, complaining of pains in all joints with swelling and fever of three days' duration. Examination showed acutely inflamed joints of the left elbow and the large toes, with redness, swelling, and tenderness. There was an apical systolic murmur. The temperature was 102° F.

The laboratory findings were: R.B.C., 3,690,000; hemoglobin, 62 per cent (Sahli); W.B.C., 16,400. The Linzenmeier tube showed a fall of the cell column to 18 mm. in nine minutes! The column in the Westergren tube fell 147 mm. in one hour! In

addition to these extremely rapid tests the Schilling smear showed 47 per cent immature forms in the blood. Thus all readings indicated a severe infection. Though these tests are not absolutely quantitative, they do in a general way suggest the severity of the infection when such evaggerated figures are obtained.

Despite these readings, after one week of rest there was a rapid improvement in all tests, the blood smear appearing almost normal. Weekly readings showed continued improvement. The temperature and pulse fell to normal one week after ad mission; the smear three weeks later; and the sedimentation tests reached high normal six weeks later (Table II). During convalescence there was a definite cosmophilia, the smear at that time being thus basophiles 2 per cent, eosmophiles 10 per cent, immature (nonsegmented) cells 10 per cent, mature (segmented) cells 36 per cent, lymphocytes 39 per cent, and monocytes 3 per cent (Chart 2).

Case 11—W. M., male, aged twelve years, was admitted March 31, 1933, complaining of pain in the spine, just below the neck, for three weeks. The pain was so severe that the boy could neither bend his head in any direction nor sleep. There was no fever on admission. Examination showed a marked stiffness of the neck with tenderness on palpation or flexion over the sixth and seventh cervical and third and fourth thoracic vertebrae. The heart was negative. Roentgenograms of the spinal column showed no abnormalities. The laboratory findings were: RBC, 4,620,000; hemoglobin, 87 per cent Sahli; WBC, 10,000. The temperature was 998°F.

The diagnosis was at first obscure. Though the temperature was normal the presence of some active infection was indicated by the Schilling count, which showed 19 per cent immature forms (cosinophiles 7 per cent, immature cells 19 per cent, mature cells 35 per cent, lymphocytes 37 per cent, and monocytes 2 per cent). Both sedimentation tests were rapid, the Linzenmeier reading twenty five minutes, the Westergren 92 mm. These figures with an cosinophilia suggested the possibility of a rheumatic infection, which was strikingly corroborated about four weeks later (April 28) with the sudden appearance of typical rheumatic nodules over the dorsum of the feet along the tendons and over the knees. At this time the Linzenmeier readings increased slightly from twenty five minutes to twenty one minutes, the Westergren remaining unchanged at 90 mm.

On May 5 a new crop of nodules appeared over both knees, at which time all tests showed increasing activity, the Linzenmeier reading seventeen minutes, the Westergren 112 mm, and the immature cells 26 per cent. On May 16 there was still some pain in the neck. The Linzenmeier reading was twenty minutes, the Westergren 77 mm, and the immature cells 29 per cent. On May 27 the Linzenmeier reading was nineteen minutes, Westergren 85 mm, and the immature cells 19 per cent. On June 7 Linzenmeier was forty minutes, Westergren 52 mm, and the immature cells 13 per cent, showing a more rapid approach of the blood smear to normal than the sedimentation tests. By June 23 the Linzenmeier reading was seventy eight minutes and the Westergren reading 25 mm. At this time, with the tests all most normal, the child was removed from the hospital

CASE 12—D G, male, aged seven years, admitted Sept 2, 1933, complained of pains in the knees and ankles for one week. The temperature ranged between 100° and 101° F. On examination the slight joint swellings were evident. There was a slight presystolic rumble and a somewhat accentuated pulmonic second sound with no definite murmurs. All tests were moderately increased. The Westergren tube showed \$1 mm, and the Cutler rate was 25 mm, in one half hour. There were 14 per cent immature cells. On September 8 a systolic murmur was heard at the apex of the heart. The Westergren reading was 111 mm, the Cutler 31 mm, and the immature cells were 17 per cent. On September 16 the immature cells were 10 per cent, but rapid sedimentation rates persisted though improved over previous read.

ings (Westergren 64 mm., Cutler 23 mm.). From September 22 to October 13, though the child was at complete rest in bed, a fulminating attack of acute rheumatic fever appeared with migrating joint swellings and rheumatic nodules along the occipital spinal column. The temperature was 103° F.

This acute phase was accompanied by joint and pericardial effusions, which subsided slowly. The temperature fluctuated between 101° and 103° F. for ten days, the pulse between 100 and 140 for three weeks. The tests on October 13, following the acute attack, were as follows: Westergren 71 mm., Cutler 28 mm., immature cells 16 per cent. On October 18 the tests were Westergren 47 mm., Cutler 18 mm., and immature cells 20 per cent, showing an unexplained increase in the Schilling count with improvement in the sedimentation rates. On October 28 the tests were Westergren 40 mm., Cutler 9 mm., and immature cells 8 per cent, showing much improved sedimentation rates with a normal smear. A marked cosinophilia occurred at this point: cosinophiles 15 per cent (!), immature cells 8 per cent, mature cells 34 per cent, lymphocytes 42 per cent, and monocytes 1 per cent.

The sedimentation tests continued to improve slowly, not reaching absolute normal until January 25, throughout which period the blood smear was within normal limits. It took more than four months for the sedimentation rates to reach normal in this case.

Case 16.—E. R., male, aged eleven years, was admitted January 19, 1935, complaining of acutely inflamed ankles, knees, fingers, wrists, and shoulders for seven days, with temperature mounting to 103.6° F. The joint involvements were migratory. Examinations revealed an acute pericarditis with a friction rub audible over the whole precordium and a double, apical, systolic murmur. R.B.C., 3,460,000; hemoglobin, 68 per cent Sahli (9.8 gm.); W.B.C., 23,200; Cutler, 31 mm.; immature cells, 30 per cent.

Despite this apparently severe involvement, in nine days the temperature and pulse were normal, the immature cells were 11 per cent, a high normal, but the Cutler reading was 29 mm., still rapid. There was a slow improvement in the sedimentation rate, which finally reached normal five weeks after the blood smear (Table II).

### CONCLUSIONS

In a convalescent case of acute rheumatic fever, with the subsidence of acute symptoms and signs, the temperature is first to fall to normal, followed by the pulse rate, then the disappearance of immature polymorphonuclear leucocytes from the blood. Last to reach normal is the sedimentation of the crythrocytes. To prevent a convalescent child from getting up too soon, this test should be the criterion of inactivity. No child should be allowed out of bed until the sedimentation test is absolutely normal. This precaution should help to diminish serious cardiac involvement in new cases and minimize increasing damage in children already affected.

## SUMMARY

The Schilling blood count and the sedimentation rate and time of the red cells have been studied in twenty normal control cases and in twenty-five children, ill with acute rheumatic fever, with and without evident cardiac involvement. The greater sensitivity of the sedimentation test as an index of inactivity has been demonstrated, and its use as a guide for completed convalescence is urged.

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# A PAPILLOMA OF THE CHOROID PLEXUS IN AN INFANT

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THE case which we are reporting is of interest because of the rarity of this type of tumor and the clinical difficulties which were presented.

Baby McL., six months old, male, was referred by Dr. Bernard W. Klippel. He was the second baby, was born spontaneously after a short labor, and at birth weighed 7 pounds and 9 ounces. He was entirely breast fed with the usual auxiliary foods. The mother stated that the baby had been happy and bright and doing nicely until a few days before admission when she noticed that the head seemed to have increased in size. It was later learned that Dr. Klippel had noticed that the head had begun to enlarge two weeks earlier than this. Vomiting had started four days before admission, and during this time he had vomited all breast feedings, orange juice, and water. He had become obstinately constipated. No known fever or illness preceded the enlarging of the head.

The baby was 27 inches long and weighed 16 pounds and 4 ounces; circumference of head was 18¾ inches which, according to the history, would indicate that an increase of about 3 inches in its size had occurred in about four days (this statement being amended at a later date by the attending physician, as stated above). Scalp veins were much distended, and the fontanel was tense, presenting the ordinary picture of an acute hydrocephalus. Besides this the baby was deeply somnolent with a pulse rate of 64. The right pupil was well contracted; the left pupil widely dilated with retinal veins definitely engorged; there was no response to light in either eye. Some slight general spasticity of the entire body was noted giving the impression of being somewhat more pronounced on the right. The abdomen was retracted and the skin doughy. The spleen was not palpable. A typical hydrocephalic cry occurred twice during the examination and supported the very strong first impression of an acute hydrocephalus most probably of tuberculous origin.

An intradermal tuberculin test using 0.1 mg. and a von Pirquet test made the day first seen were negative. A Schilling differential blood count showed a normal, noninfectious picture which, with the absence of a palpable spleen, immediately brought the original impression of tuberculous meningitis into very serious doubt. Besides this, a spinal tap on the following day by Dr. Klippel showed a clear, free-flowing fluid under increased pressure with a normal cell count and a negative Pandy test; no pellicle formed on standing. No organisms were found on smear, and cultures of the fluid were negative. Following the tap, the pupils became equal.

In reviewing this with the history covering the four days, as given by the mother when first seen in the office, one is impressed with the clinical interest attaching to an apparently justifiable diagnosis of tuberculous meningitis, which despite an array of well-complemented signs was not sustained but, to the contrary, could be set aside by the laboratory findings and by the fact that in such cases one feels that he should often be able to detect an enlargement of the spleen. The situation thus became a very puzzling one.

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Read at a meeting of Regions II and III of the American Academy of Pediatrics,

## AUTOPSY

The baby died ten days later and permission was obtained for examination of the cranial contents only. The fontanels were both wide open and tense, the head showing the typical form of an hydrocephalus. When the skull was opened, the convolutions of the brain, especially over the left parietal and occipital regions, were found to be markedly compressed and atrophic. The brain ruptured spontaneously as it lay on the table, the rupture having occurred through a thinned area in the brain tissue of the left parietal region. A small opening here emitted a large stream of thin, clear, straw-colored fluid which was found to be escaping from the greatly distended posterior half of the left lateral ventricle. There was a reddish papillomatous tumor about the size of a large biscuit arising in the base of the central portion of the left lateral ventricle just posterior to the foramen of Monro and extending through the ventricular cavity where the tumor, together with a flat strip of brain tissue, formed a partition dividing the ventricle into an anterior and a posterior chamber. There was no opening between these two chambers. Both were distended but the posterior portion was distended to such a degree that it gave the impression of being an enormous thin-walled cystic cavity. The foramen of Monro

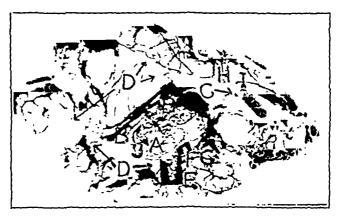


Fig. 1.—Photograph of brain: A, showing encapsulated papilloma arising from a narrow strip of brain tissue; B, forming a partition in the lateral ventricle; C, anterior chamber, and B, posterior chamber of left lateral ventricle; E, F, and G, three pieces of choroid plexus attached to the tumor. The majority of the "seed" metastases were situated in the anterior wall of the strip of brain tissue, B, near the base of the tumor. (These do not show in the photograph.) H shows where a block had been taken including a "seed" metastasis; I, a small "seed" metastasis; J, capsule of the tumor.

was blocked by the tumor lying over its orifice, causing the anterior portion of the ventricle to become somewhat distended. The tumor had caused some pressure atrophy of the lateral wall of the right lateral ventricle although the septum pellucidum was intact. The pons and medulla were markedly flattened, and there was a distinct pressure collar on the inferior cerebellar surface. The left oculomotor nerve was imbedded in a mass of soft edematous connective tissue. Three small pieces of choroid plexus projected from the main tumor mass, their free ends floating in the anterior chamber of the lateral ventricle. The tumor was completely covered over with a thin enveloping membrane which was continuous with the ependyma of the anterior chamber of the left lateral ventricle. The three segments of choroid plexus which arose from the tumor were apparently not covered over by a membrane. There were eight or ten small implant "seed" metastases in the wall of the anterior portion of the left lateral ventricle. The majority of these were situated immediately adjacent to the main tumor mass in the base of the ventricle although they

were distinctly separate masses. There were also two small "seed" metastases on the superior wall. These "seed" metastases were not found in any other portion of the brain. These secondary tumor masses did not appear to be covered by an enveloping membrane as was the main tumor.

Microscopic sections of the tumor showed it to be a papillomatous tumor composed of branching villi in orderly arrangement with central cores of loose, or sometimes dense, connective tissue in which there were imbedded small thin-walled blood vessels, the epithelial cells which covered the villi being arranged usually in single layers, although in some cases several layers were present. The cells were well differentiated, and no mitoses were seen among them. They were either low or high cylindrical cells with oval or round nuclei situated near the base of the cells. With phosphotungstic acid hematoxylin stain the cells showed coarse, darkly staining mitochondria in the cytoplasm which in some cases were arranged around the nuclei. No glia fibers were present in the tumor, and no blepharoplasts were seen.

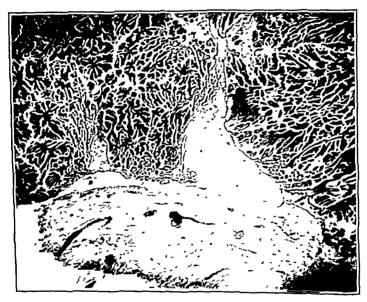


Fig. 2.—Low power photomicrograph of the main tumor mass, showing the fibrous tissue stalk of the papilloma at the site of origin from the brain tissue. (H & E stain.)

In spite of the fact that the tumor cells appeared to be very well differentiated, there were occasional small papillomatous and glandlike masses of tumor cells which had invaded the surrounding brain tissue at the base of the tumor to a very slight degree. The sections of the wall of the posterior segment of the ventricular cavity showed it to be lined with a layer of typical ependymal cells.

## DISCUSSION

This tumor was considered to be a typical papilloma of the choroid plexus arising from the plexus of the left lateral ventricle. These tumors are relatively uncommon although they are well known in the neuropathologic literature. Davis and Cushing¹ reported six cases in a series of 964 intracranial tumors, a percentage of 0.6 per cent. Van Wagenen² in 1930 made an exhaustive review of the literature,

carefully analyzing forty-five cases and adding two of his own. Sachs<sup>3</sup> was one of the first to report a successful surgical removal of one. Although these tumors are typically localized, van Wagenen<sup>1</sup> studied the question of "seeding" and found that in six reported cases this had occurred. Although our case did not show nearly the widespread seeding which occurred in van Wagenen's case, it did show definite small "seed" metastases in the wall of the anterior chamber of the left ventricle.

An unusual feature of this tumor is the fact that it, together with a strip of brain tissue from which it had its origin, formed a complete partition in the left lateral ventricle causing the posterior portion of the ventricle to be completely separated from the anterior portion, leaving no opening between the two chambers. The fact that the posterior part of the ventricle was so extensively distended suggests that the tumor "secreted" cerebrospinal fluid. There was no choroid plexus in the distended posterior portion of the left lateral ventricle, and, since the cyst was filled with what appeared to be cerebrospinal fluid, it seems reasonable to assume that the fluid had its origin from the tumor. The majority of the reported cases have been cystic tumors,2 and the suggestion has been made that the cysts contain cerebrospinal fluid which had been "secreted" by the papillomatous tumors.

An additional feature emphasized by van Wagenen<sup>2</sup> and borne out in this ease, was the fact that papillomas which occur in the lateral ventricles are particularly likely to have an enveloping membrane about them. This feature is very striking in our case.

Another unexplained and curious fact is that this tumor, as well as 93 per cent of the papillomas arising in the lateral ventricles collected by van Wagenen, occurred on the left side.

## SUMMARY

A case is reported in which a presumptive diagnosis of acute hydrocephalus of tuberculous origin was based upon the history as given by the parent and the clinical signs. It was found instead to be the result of an enormous distention of the lateral ventricle caused by a papilloma of the choroid plexus which arose from the floor of the ventricle and obstructed the foramen of Monro on one side. The importance of the Schilling differential blood count, the spinal fluid examination, and the need for considerable reserve in the diagnosis of acute hydrocephalus are emphasized in this case, as well as the necessity of avoiding pitfalls of this sort that the surgeon might save a life.

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# A SIMPLE MECHANICAL METHOD FOR THE TREATMENT OF ENURESIS IN MALE CHILDREN

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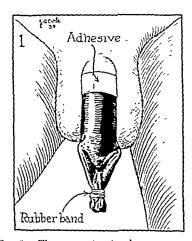
E NURESIS is one of the most common disorders encountered in pediatric practice. While its etiology may be found at times in anatomic or physiologic abnormalities, a review of which is beyond the scope of this communication, the great majority of pediatricians believe the disorder to be of functional origin, based in most cases on faulty habit training or other abnormal psychologic states. The reason pediatricians hold this belief is that most children can be cured of enuresis by the methods ordinarily used, perhaps the most common being that of awakening the child at regular intervals during the night and making him go to the toilet fully awake with the knowledge of why he has been awakened. The fundamental basis of success in this method is making the condition a nuisance to the child as well as to the parents, and thus stimulating in the child a desire to control his bladder. Other methods—as forms of bribery, in which a reward is promised for success, reasoning with the child, appealing to his pride, a change of environment—all procedures affecting purely the psyche, also occasionally meet with success.

Various mechanical measures have been devised from time to time and have met more or less success, but there is no one mechanical method which has met with universal approval. The procedure about to be described resulted from the constant stimulus of a mother driven desperate by the constant bed wetting of her seven-year-old son, who, according to her, had not missed a night since he was born. reviewing the literature in the attempt to find some method of controlling this boy in whom all procedures had met with failure, we were impressed by the communication of Bonjour. He stated that the best method of treating the condition is by hypnotism, which is impractical in childhood. He reported success by sealing the prepuce with adhesive. If this is properly done, urine does not escape from the urethra, and when the bladder is full enough to give rise to a sensation of discomfort, the child will awaken and in this manner gradually be educated to control the bladder. Girls were treated similarly by sealing the labia majora together with adhesive.

After a number of experiments the following modification of this method was adapted for the use of male children. A section of Pen-

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rose rubber tubing of a size which will slip comfortably over the shaft of the penis is chosen. This is cut so that, when fitted over the length of the penis within 0.5 inch of its base, the free end will project from 2 to 2.5 inches beyond the tip. The tube is sealed to the base of the penis by means of an adhesive band covering both the rubber and the skin. This is the most difficult part of the technic, for, if improperly done, leaks readily occur here. The free end of the tube is closed by folding over about 1 inch and sealing this by means of a small rubber band. The details of the procedures are illustrated in Figs. 1 and 2. The method is explained to the child who can in most cases readily understand why, with this "raincoat" in place, he cannot possibly wet the bed; this suggestion is very important for the early success of the method. If, after the child goes to bed, urine is passed into



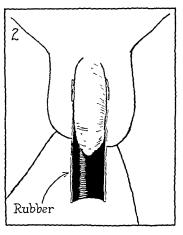


Fig. 1.—The apparatus in place. Fig. 2.—Hemisection of the rubber tube and adhesive showing their relationship to the penis.

the rubber tube, it cannot escape into the bedclothes, and he awakens either, as it is usually expressed, from a sense of weight between his thighs or because of the feeling of a distended bladder. He may then either call his parent or, preferably, go to the toilet himself, release the rubber band at the end of the tube, pass his urine, and go back to bed. Older children may be taught to reseal the tube with the small rubber band.

This simple method succeeded brilliantly in the original case which stimulated its application, as well as in a number of other cases of persistent enuresis. We believe, however, that, while in some cases success is obtained because of the mechanical principles involved, in most cases the effect of the method is psychologic. Many boys cease wetting the bed after the first application of the tube without ever having wet it. The method will not succeed in the case of feeble-

minded children who cannot cooperate or so-called normal children who will not cooperate. It is too easy to tear the rubber or loosen its connections. We are assured by a competent genitourinary authority that the danger of infection from backflow of urine into the bladder is negligible. The tube does not appear to cause or increase a tendency to masturbation. We have had no experience with the application of the principles of this method in girls.

233 OXFORD STREET

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## ATRESIA OF THE VULVA IN CHILDREN

PRESTON NOWLIN, M.D., AND J. R. ADAMS, M.D. CHARLOTTE, N. C.

DURING the past two years we have encountered several cases of cohesion of the labia minora in young females. Due to the apparent frequency of this condition and due to the fact that it may be a factor in producing chronic urinary obstruction, this anomaly deserves consideration.

In American literature there has been little mention made of the condition. The standard pediatric and urologic texts do not refer to it. One of us, in 1934, reported one case in a child twenty-five months of age.

The foreign literature is fairly extensive. R. Lederer, in 1929, reported a case in a child two years of age. In 1930, Vakar reported fifteen cases of this type seen in one year, the ages ranging from three months to two and one-half years. In 1934, H. Schlack reported six cases. There have been other reports in the Italian and in the French literature which have not been available to us. Cases persisting into adult life have been reported by J. B. Hellier in 1914 and Margaret Salmond in 1930.

### ETIOLOGY

The question arises as to whether this condition is congenital or acquired. We have never seen it in the newborn. Two of the patients reported here were examined at birth, and the genitals found to be normal. These facts would lead us to believe it is an acquired and not a congenital anomaly.

In the development of the female genitals each of the labia minora is developed separately from a genital fold. These genital folds are developed from the lips of a groove on the extremity of the genital tubercle, a structure which appears approximately in the fifth week of life. Since at no time during development is there fusion of the genital folds, one might assume that atresia of the vulva is not due to any inhibition of normal development in the embryo as is the ease in atresia of the vagina.

None of these cases has given any history suggesting either a gonorrheal or a nonspecific vulvitis, and in none was vulvitis present at the time of the examination. However, due to the richness in cellularity of the labia minora in young girls and due to the fact that the labia minora lie in close contact in early life, particularly in the posterior portion, it is probable that a very mild inflammatory reaction might later cause an agglutination of these structures without any marked signs of a vulvitis.

From the Nalle Clinic, Charlotte.

Vakar believes that in the cases studied by him there must have existed previously a vulvovaginitis or a vulvitis. In 47 per cent of his cases vulvitis was present at the time of examination. In his opinion the physiologic desquamative vulvovaginitis of the newborn plays an important rôle, in that this physiologic catarrhal inflammation may serve as a predisposing factor for the penetration of pathogenic organisms, which is eventually followed by infection and adhesions.

From the above it would appear that the described anomaly is post-inflammatory in character following a previous mild vulvitis. The fragility of the adhesions found would tend to bear out this contention.

## SYMPTOMS AND SIGNS

Two of the cases reported have presented no symptoms referable to this disorder, the condition being found as a part of routine examination.

Urinary disturbances, found expressed in the form of interruption of the stream, were observed in six of these cases. Tenesmus and frequency were present in all of these. In one case a chronic pyelocystitis of nine months' duration was apparently due to this form of obstruction. Residual urine in the bladder and in the vagina was noted in this same case. No pruritus nor tendency to masturbation has been noted by us. In this small series, the youngest noted was eighteen months old and the oldest three years old.

On physical examination the condition is easily recognized. On separating the labia majora, the labia minora are found sealed together by a thin, bluish, almost transparent membrane. Anteriorly there is a small pinpoint opening just below the clitoris through which the urine is passed. This opening is posterior to the clitoris, but well anterior to the external urethral orifice, so that in effect there is a diaphragm which tends to obstruct efficient emptying of the bladder. In two of these, two to three minute perforations in the membrane were seen in about the midposition.

Micturition in one case was accomplished only with great difficulty; the child apparently filled the vagina with urine and then slowly expelled it through the opening below the clitoris.

#### TREATMENT

Simple separation of the labia minora has been effective in these cases, accomplished either manually or by use of a probe. The slight bleeding which occurs is easily controlled by pressure. A bland ointment is prescribed to prevent agglutination of the raw edges. We have so far seen no recurrences.

## CASE REPORTS

CASE 1.—B. G., aged two and one-half years, was seen Nov. 14, 1933. For nine months she had had frequent attacks of "pyelitis," characterized by high fever, vomiting, abdominal pain, and marked frequency of urination. The attacks occurred about every two weeks and lasted from three to five days. Her urine had been examined frequently and was always found loaded with pus. Varied medication had been given without benefit. The patient had lost weight, had a poor appetite, and was extremely irritable.

Examination revealed a thin, active child, not acutely ill. She weighed 25 pounds. The temperature rectally was 99.4° F. Abdominal findings were limited to the genitals. When the labia majora were separated, the labia minora were found to be adherent throughout, except for a purpoint opening posterior to the clitoris but well anterior to the wrethra. Traction on the labia produced the appearance of a thin, semitransparent membrane completely occluding the introitus. During the examination a small amount of urine was passed with obvious effort. The adhesions

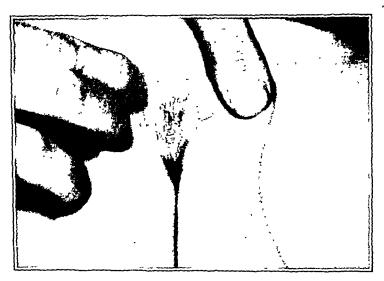


Fig. 1.-Case 3. Atresia vulvae.

were separated digitally and boric acid omtment applied to the denided surface. A 10 F catheter was passed into the bladder and 80 c.c. of residual urine obtained. All symptoms immediately disappeared, and there was been no recurrence over a period of eighteen months.

CASE 2.—T. O., aged three years, was seen on Jan. 18, 1934, because of fever, pain on urmation, and frequency of four days' duration. The urine was loaded with pus. General physical examination was negative, but on separation of the labia majora complete atresia of the labia minora was found, with a minute opening posterior to the chtoris, as in the above case. Manual separation was performed with case. Symptoms subsided promptly, and there has been no recurrence in over a year.

CASE 3.—G. D., age two and one-half years, was seen on May 16, 1935, because of listlessness, poor appetite, and painful frequent urination of two days' duration. On examination the labia minora were found adherent throughout except for a small opening adjacent to the chtoris (Figs. 1 and 2). This child had been seen

regularly since birth, and the adhesions were known not to have been present up to four months before this examination, when she was last seen. Prompt disappearance of symptoms followed separation of the labia, and there has been no recurrence to date.

CASE 4.—M. G., aged eighteen months, was seen on Feb. 5, 1934, because of frequent painful urination of two days' duration. Examination disclosed labial adhesions as described above, and separation was followed by prompt cessation of symptoms. This child, too, had been seen regularly since birth and is known to have been normal up to four months before the present examination.

CASE 5.—B. C., aged six months, was seen on March 11, 1935, because of frequent, painful urination. Labial adhesions closed the entire introitus except for a small opening adjacent to the clitoris. Manual separation was performed with ease, and all symptoms promptly subsided.

CASE 6.—S. O., aged five months, was seen on Nov. 25, 1934. For about a week she had cried out on urination, as though in severe pain. So far as the mother

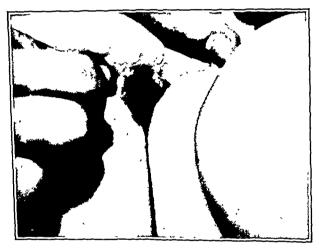


Fig. 2.—Case 3. Condition after separation of the labia minora.

knew she had had no fever. Examination was negative except for complete adhesion of the labia minora, as in the above cases. There was only a pinpoint opening present. After the labia were separated with a probe, the symptoms cleared up quickly.

CASE 7.—J. H., aged seven months, was seen on Nov. 30, 1933, for routine examination. The labia minora were found adherent throughout except for a small opening next to the clitoris. There had been no symptoms. Separation was accomplished easily with a probe, and to date there has been no recurrence of the adhesions.

Case 8.—G. S., aged nine months, was seen on May 8, 1934. She was perfectly well and had no urinary symptoms. Routine examination revealed labial adhesions as described. The adhesions were separated with a probe and have not returned to date.

## CONCLUSIONS

1. Eight cases of atresia vulvae or cohesion of the labia minora have been observed in the past two years.

- 2. The condition seems to be acquired rather than congenital and is not associated with any other defect.
- 3. Treatment consists of separation of the labia minora either manually or by use of a probe.
- 4. The condition may be asymptomatic or may produce symptoms of urinary tract obstruction.

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412 N. CHURCH STREET

# CALCIFIED ABDOMINAL GLANDS IN CHILDREN

## A CLINICAL STUDY

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DESPITE the numerous publications on the occurrence of calcified abdominal glands and the symptoms which may arise from them, questions as to the management and prognosis of this syndrome continue to be difficult to answer. The present study was undertaken in an attempt to evaluate our experience with this clinical finding in 147 children seen in the medical and surgical clinics and the private ward of the Children's Hospital.

In older works on tuberculosis of the mesenteric glands emphasis was placed upon states of actual inflammation, the so-called "tabes mesenterica." This condition as a clinical entity is apparently less frequently seen than formerly. It is not dealt with in the present paper. the other hand, interest in calcified and supposedly inactive abdominal glands has been increasing since Dunham and Smythe1 pointed out the accuracy and ease with which such glands could be identified roentgenologically. The literature contains numerous case reports of acute and chronic abdominal symptoms and diagnostic problems arising from such glands.2, 3, 4, 5, 6 Their etiology and epidemiology as unsuspected, nonthoracic foci of tuberculosis have been discussed in another paper.7 Finally there have been a few general analyses of large groups of cases from all approaches. The reader is referred particularly to the monograph by Strömbeck,8 in which a full bibliography will be found. attempt at such a review is made in the present communication as much of the literature is repetitious or consists of reports of single or few Some authors combine the three subjects of nontuberculous mesenteric adenitis, active tuberculosis of mesenteric glands, and calcified mesenteric glands. It should be repeated that the present study is concerned only with children who present the last-named condition.

Our material consists of the records of 147 children with demonstrable calcifications of the abdominal glands, seen at this hospital during the past ten years. By questionnaires and return visits the present status of all but sixteen of the group has been determined. While our main interest has been in determining whether and in what manner these glands affect the well-being of children, and how they should be treated, we have been secondarily interested in their frequency, their relationship to other tuberculous processes, and their original source of infection.

From the Departments of Pediatrics and Surgery, Harvard Medical School, and the Children's and Infants' Hospitals.

## ETIOLOGY AND ROENTGENOLOGIC APPEARANCE

Various conditions may produce abdominal shadows of calcium density, but an old tuberculous infection of the mesenteric glands would appear to be much the most common one in childhood. We have tried to exclude from our study children in whom there were evidences of some cause other than the tubercle bacillus. In all children who were tested with tuberculin (119 of the series) the reaction was positive. It is difficult to give exact data as to the frequency with which the condi-



Fig. 1 A.

Fig 1.4 and B—Numerous calcifications in chest, abdomen, and pelvis of a girl of 11. Recurrent abdominal pain for one year before. At 18 years is still having mild and intrequent pain. Note calcified gland to right of lower coccyx. (See opposite page for Fig. 1B)

tion occurs. It appears to vary considerably with the locality in which surveys are made, as has been pointed out in the literature. 1, 2, 7 From our experience and from that of Dunham and Smythe1 and Gibson,7 the frequency must be comparatively high in southern New England. At the Infants' and Children's Hospitals, such glands have been found in between 1 and 2 per cent of abdominal roentgenograms of patients between the ages of two and twelve years. Obviously, when such examination is confined routinely to tuberculin-positive children, the percentage may be considerably higher,

Because the child who presents this condition must be considered as having a past or potential tuberculosis, it is of interest to consider the relationship of these glands to tuberculous processes elsewhere in the body. In the majority of our patients we have roentgenologic data as to the condition of the chest. These are summarized in the first part of Table I; in the second part are given data on the nonthoracic tuberculous



Fig. 1B -See legend under Fig. 1A.

lesions of the group as a whole. Examination of Table I shows that, while some evidence of old pulmonary and hilum tuberculosis was found, there was only one child in whom this seemed to be active. We have seen no pulmonary or hilum tuberculosis develop in the subsequent course of any patient. There were a few children whose chest x-rays showed several scattered pulmonary and regional hilum calcifications.

In such cases the abdominal plates often showed numerous areas of calcification (Fig. 1 A and B). These children apparently had at one time a widespread tuberculous infection, though, because of the equal degree of calcification in the chest and abdomen, it is not possible to state whether infection in either region was secondary to that in the other.

As shown in the table, some of the evidence of intrathoracic tuberculosis was considered by the roentgenologist as questionable. There was definite positive evidence in a total of fifteen patients, or 13.8 per cent of those whose chests were x-rayed. The association of nonthoracic tuberculosis occurred in a larger number (twenty-six) of the 147 children. In cases in which this infection was in the bones, joints, cervical glands, skin, or bowel, it apparently preceded the abdominal glandular lesions or was contemporaneous with them, with the exception of one child in whom a tuperculous lesion developed in the right acetabulum a few months after calcium was first found in the abdominal plate.

TABLE I
TUBERCULOSIS ASSOCIATED WITH CALCIFIED ABDOMINAL GLANDS

NONI		61	ABLE OF STREET		old active		TOTAL DEFINIT THORACI LFSIONS			
Number Per cent of 109	83 76		11 10.1		14 12.8	1 (hil 0 9		1) 15 13 S		
B Nonthoracic (History and Examination of 147 Children)										
	NOVE	CFR\10\L GL\\DS	BONES IND	PFRITOVITIS	SKIN	INTP STIN VE	MEVINGFS	TOTAL Nonthoracic		
Number Per cent of 117	121 82 1	9 6 1	6	7	1 0.7	1 0 7	2	26 17.6		

It will be noted from the table that two children had tuberculous meningitis. These represent the only deaths from tuberculosis in the entire series. In both, the calcifications were first discovered at the time of admission with meningitis and had produced no local symptoms. One patient was a girl of five years, who showed no clinical or roentgenologic evidence of tuberculosis except in the meninges and abdominal glands. The glands were solidly calcified. The other child was an infant of eighteen months, heavily infected from a consumptive mother. A large pulmonary infiltration had been noted in this child's chest a year before. It had cleared almost entirely at the time meningitis and early calcification of glands were discovered. Unfortunately, autopsy

was not permitted in either child. No miliary dissemination was discoverable by x-ray plates in either one. It seems probable that in both of them the meningitis arose from an isolated tuberculoma in or near the central nervous system. It would seem unlikely that an abdominal focus could give rise to meningitis without also producing a generalized miliary spread.

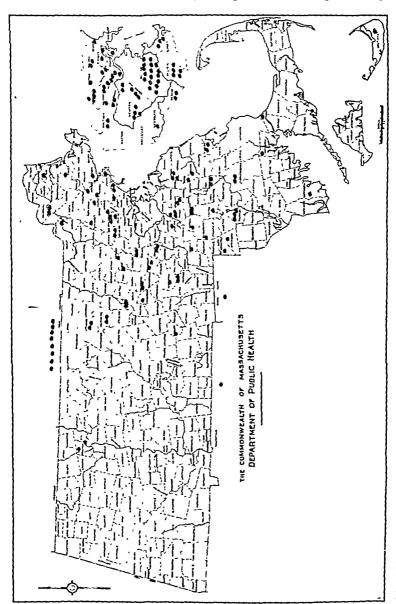
The association of manifest tuberculous peritonitis deserves separate comment. It was present in seven of our patients. In all of these the peritonitis was observed in the hospital. In two of the seven children, calcium was first found in the abdomen from four to five years later; in the other five, the conditions were found simultaneously, and in them the calcification consisted of a partial fleeking or outlining of the gland as shown by roentgenogram. In our experience tuberculous peritonitis has not developed in any child after the presence of calcified glands was discovered. This statement is based on the 131 children we have been able to follow, of whom fifty-two have been under observation for from six to ten years. We infer that while glands which are beginning to calcify may disseminate bacilli to the peritoneal surfaces, a child whose roentgenograms show solidly calcified shadows is in little if any danger of peritoneal involvement. Our findings also indicate the likelihood that associated tuberculous lesions usually arise from the same source as that responsible for the mesenteric gland infection rather than as later secondary disseminations from these glands.

Certain evidences are shown in patients in this series that the source of infection is often contaminated milk. There was a rather infrequent history of household contact with tuberculosis. This background was definite in only fifteen children (10.2 per cent), doubtful in an equal number, and absent in 117 of the group. Of the fifteen known contacts, six were with persons with bone, gland, or renal tuberculosis. It is possible that the members of these families may have acquired their infection through the family milk supply. We have less data concerning the milk supply of the total group than concerning their exposures, but in the forty-seven instances in which this is recorded, there was a history of raw milk in the diet of thirty-four patients.

The children have in general come to the hospital from the smaller outlying communities, where milk production is often unregulated. Figure 2 shows the distribution of their homes as contrasted with those of a comparable group seen in the hospital with primary pulmonary tuberculosis in the same period of years. A much larger number of the latter group have come from the city of Boston, where, though chances for contact with diseased individuals is greater, the milk supply is well controlled. Twenty-two children in our series were patients in the private ward, and are included in this study through the courtesy of their private physicians. It is possible that these children, from the

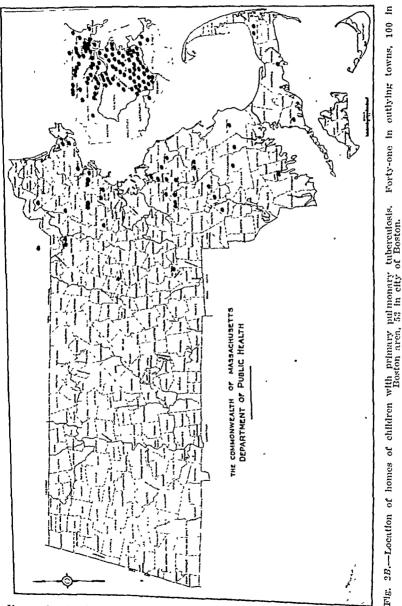
more fortunate social classes, have had opportunities to visit in rural districts where there is less pasteurization of milk.

The evidence that ingested tubercle bacilli may pass through the intestinal wall to the associated lymph glands without producing actual



Pig. 2.1.—Location of homes of children with enicified abdominal glands. Eighty-five in outlying towns, 68 in Boston area (in insert), 17 in elty of Boston.

intestinal lesions is considerable. In only one of our patients, a boy aged ten years, do we know of the presence of bacilli in the stools. This child had a history of passing bloody stools for a period of five months before he came to the hospital. His tuberculin test was positive; the roentgenograms of the chest were negative; and a flat plate of the abdomen showed several calcified glands. He was withdrawn from the hospital before our own bacteriologic study of the stools was completed, but a tentative



tuberculosis. Forty-one in outlying towns, 100 of Boston.

diagnosis of tuberculous colitis was made although two examinations with barium by rectum and one with barium by mouth were negative. went, after a few weeks, to another hospital where blood and tubercle bacilli were repeatedly found in the stools, and he recovered without further evidences of tuberculosis on a routine sanatorium treatment. This is the only one of our patients in whom evidence of actual intestinal lesions was present, and we cannot be sure that in this child the active intestinal lesions stood in a causal relationship to the calcification in the glands, or that the reverse might not have been true.

In a study of necropsy material, Leonardo found intestinal lesions in only a third of forty-eight children, all of whom showed tuberculosis of the mesenteric glands. Moreover, it is of interest to note that while there is usually a considerable involvement of the abdominal glands during the course of a true tuberculous peritonitis, in two of our patients with peritonitis only three calcified glands could be demonstrated in the abdomen four years later. There must frequently be lesions of tuberculosis in abdominal glands and possibly in the intestinal wall, which heal perfectly or at least become entirely quiescent. In the case of the glands, it is likely that this may occur without any ultimate calcification. At all events, we feel that a child whose roentgenogram of the abdomen shows calcified glands usually represents an original tuberculous infection by ingested bacilli. Unless such a child continues to ingest bacilli, the danger of further and more active tuberculosis elsewhere in the body would appear to be slight. The possibility of meningeal involvement from an associated lesion can never be ignored.

The roentgenologic appearance of calcified abdominal lymph nodes has been described many times and is quite typical. In a child with one doubtful shadow, a second examination made after a few days, and with the bowel empty, is obviously an essential procedure. With the corroborative evidence of this procedure and a positive tuberculin test, there have been no cases in our series in which the diagnosis was in doubt. The shadows range in size from flecks of a few millimeters, often grouped in small aggregations, to ringlike or irregular "mulberry" shadows up to 2 cm. in diameter, and sometimes larger. We have found as many as twenty in one film (Fig. 1 A and B), though most frequently there are from one to three. Tabulated data as to roentgenographic findings in the two largest groups of patients are given in Table II and will be referred to later.

# CLINICAL FINDINGS

In studying our 147 patients from the point of view of their symptoms and treatment, we have first subtracted the seven patients who had at some time tuberculous peritonitis. These children have been discussed above. This leaves 140 children in whom the findings may be laid more definitely to the glands themselves (Table III). The first group of these contains sixty-nine children who were symptom free or presented complaints explained by other findings than the glands. The second group

contains seventy-one children with symptoms, unexplained except by the presence of calcified glands.

TABLE II

RELATION OF PAIN TO NUMBER, SITE, SIZE, AND DEGREE OF CALCIFICATION OF GLANDS
IN AVAILABLE ROENTGENOGRAMS (PERCENTAGES IN PARENTHESES)
GROUP I—64 CASES WITHOUT SYMPTOMS
GROUP II—59 CASES WITH PAIN

		A. Number	of Glands						
	1	2	3	4	MORE THAN 4				
Group I	12 (18.8)	17 (26.3)	13 (20.4)	4 (6.2)	18 (28.2)				
Group II	18 (30.5)	14 (23.8)	17 (28.8)	3 (5.1)	7 (11.8)				
Totals	30 (24.4)	31 (25.2)	30 (24.4)	7 (5.7)	25 (20.4)				
	B. Size of Largest Gland Shadow								
	UNDER 5 MM.		10-20 мм.		AN 20 MM.				
Group I	7 (10.9)	18 (28.2)	27 (42.2)	12	(18.7)				
Group II	4 (6.8)	18 (30.5)	31 (52.5)	6	(10.2)				
Totals	11 ( 8.9)	36 (29.2)	58 (47.2)	18	(14.7)				
	C. Region of Abde	men*	D. 1	Degree of Co	alcification*				
		DDLE LT.	FLECK	S OUTLIN	E SOLID				
Group I	45 (62.5) 3	(4.2) 24 (33.	$\overline{3}$   $\overline{17}$ (23.	9) 38 (53.	5) 16 (22.6)				
Group II		(3.0) 27 <b>(</b> 40.	4) 24 (38.	7) 24 (33	7) 14 (22.6)				
Totals	83 (59.6) 5	(3.6) 51 $(36.$	8)   41 (30.	8) 62 (46	6) 30 (22.6)				

<sup>\*</sup>Different types of glands in the same plate are each listed.

Somewhat more than half of all the patients were girls. The youngest child was the eighteen-month-old boy, who had tuberculous meningitis at the time the calcified glands were discovered. In autopsy studies Leonard<sup>9</sup> found calcification in the mesenteric glands of infants as young as six months. The average age of our patients at the time of the first positive roentgenogram was 7.7 years.

The first group of sixty-nine children need be mentioned only briefly.

TABLE III
DISTRIBUTION OF CASES

CLASSIFICATION	NUMBER	%	вочѕ	GIRLS	AVERAGE AGE AT DISCOVERY OF GLANDS
WITH PERITONITIS	7	4.7	4	3	6.4 YR.
<ol> <li>No symptoms</li> <li>Symptoms unexplained</li> </ol>	69	46.9	30	39	7.6 yr.
except by glands	71	48.4	30	41	8.4 yr.
Totals	147	100	64 (43.5%)		

They are of importance as an indication of the frequency with which unsuspected tuberculous infection may leave a residue of asymptomatic calcium in the abdomen. That the outlook in such children is good is shown by our follow-up of these patients. We have followed twenty-six for a year or less, twenty-five for one to five years, and eighteen for six to ten years. Three have died of nontuberculous disease, one of

sepsis, one of leucemia, and one of malignant lymphoma. Two others died of tuberculous meningitis as mentioned above. Of the remaining sixty-four, three have developed occasional mild abdominal pains. In one of these the symptoms cleared after recurring for one year. In the other two there are still transient pains. In the great majority of the group the glands have never given rise to symptoms or alterations in healthy growth, and these children have received no antituberculous treatment beyond general hygiene and advice to the parents as to the safety of the milk used. Thirteen children in this group had been operated on at some time for appendicitis. The glands occasionally were discovered in preoperative roentgenograms. In all these patients the pathology in the appendix explained the symptoms which led to operation, and such symptoms were relieved thereafter.

The seventy-one children with symptoms attributable to the glands form our largest group. Table IV shows the duration and ultimate outcome of symptoms in this group, as well as the length of the time we have observed them since the first discovery of calcified glands. Several are now in their later adolescence, and a few are over twenty years of age. The majority of those whose symptoms are listed as not having cleared are only mildly or occasionally disturbed by them.

TABLE IV
PRESENT STATUS OF CASES WITH SYMPTOMS

DURATION OF SYMPTOMS	, -	OVER 2 Yr.		1-2 YR.		6-12 мо.		1-6 мо.		UNDER 1 MO.	
STATE OF SYMPTOMS	CLEARED	PRESENT	CLEARED	PRESENT	CLEARED	PRESENT	CLEARED	PRESENT	CLEARED	PRESENT	
Followed 6-10 yr. (33)	6	S	4	0	4	0	5	0	6	0	
Followed 3-5 yr. (6)	0	1	1	1	1	- 0	0	0	2	ñ	
Followed 1-2 yr. (13)	1 0	0	G	1	2	0	2	Ö	9	0	
Followed 6-12 mo. (9)	1	0	0	0	2	0	5	0	1	Ô	
Followed less than 6 mo. (10)	2	0	1	0	1	0	0	0	6	0	
Totals (71)	9	9	12	2	10	0	12	0	17	0	
Totals	1	$\mathbf{s}$	' 1	4	10	o j	19	? ;	1	7	

In sixty-three of these children the main complaint was of abdominal pain. While the manifestations of such a symptom in such a large group of cases are too varied for description or tabulation, a few short case abstracts will suggest the ordinary picture:

CASE I.—M. F., a girl six years old, was brought to the hospital because of abdominal pain for six months. There was a history of the use of raw milk from a nontested herd. The family history was negative. Pain had occurred in attacks lasting from a few minutes to half an hour, almost daily, unrelated to meals. It was localized to the midabdomen, was severe enough to make her double up and had been associated with vomiting only three times. Tuberculin test was positive: roentgenograms of the chest were negative; those of the abdomen showed

several large calcified glands to the right of the midabdomen (Fig. 3). With rest in bed for the next three months, pain became more transient but persisted. At one time slight spasm was found in the right lower quadrant, and a few indefinite masses were palpated there. During the next year with increasing activity allowed, pains became as rare as only twice a month with occasionally more frequent recurrences. Three roentgenograms during the year showed no change in the abdomen. Her general physical condition has been steadily good. She is still under observation, but not seriously disturbed by her pains.

Case 2.-J. Mi., a nine year-old boy, had received raw milk for two years after wearing; there was no tuberculosis in the family. Eight months before admission



Fig. 3.—Case 1 in text. Calcified glands associated with recurrent abdominal pain in a girl six years old. Responding to rest and hygiene.

he had suddenly been seized with severe cramping abdominal pain while playing. This lasted ten minutes. Since that time he had complained of similar pain once or twice weekly, usually brought on by running or overeating, and occasionally radiating to the left lower quadrant. Vomiting had occurred once. Examination of the abdomen was negative, as was the general physical examination. Tuberculin was positive; a chest roentgenogram showed a little calcium at the hilum, and a flat plate of the abdomen showed a large mass of calcified glands in the right lower quadrant (Fig. 4). He was sent home on a modified rest regime, on which he was tree of pain until six weeks later, when he had severe abdominal pains most of collowed for nine months without pain.

Case 3.—J. Me., a boy aged two years and three months. Three of his siblings had been seen in the hospital, one with tuberculous peritonitis, one with tuberculous hip disease, and one with calcified abdominal glands. He was admitted to the ward because of painless abdominal distention of two days duration, which responded to an enema and did not recur during two weeks of observation, or thereafter. The spleen and have were palpable. Tuberculin test was positive; a film of the abdomen was negative at this time, and one of the chest showed peribronchial congestion. Advice as to safeguarding the family milk supply was given.



Fig. 4.—Case 2 in text. Nine-year-old boy with symptoms of recurrent pain on exertion, ceasing on moderate rest therapy.

He had no symptoms for seventeen months and then began to have attacks of abdominal pain two or three times daily, severe enough that he sometimes cried out with it. It was not related to food or to the state of his bowels, and he did not vomit. After a month of this pain he was reexamined. There were no findings except that a repeated film of the abdomen showed a large partly calcified gland to the right of the fourth lumbar veitebra. Treatment consisted of moderate rest and sun baths. In nine months since then he has laid only one attack of pain.

These three children illustrate the tendency of the pain to be recurrent over prolonged periods of time, without relationship to meals, and to be brought on by fatigue or strain. Its location and the findings upon physical examination are discussed below. Besides their pain, these patients have sometimes been nauseated, and in a few instances there have been severe attacks of vomiting. With acute attacks of pain, parents have sometimes reported that the children were feverish, but temperatures above 100° F. have not been seen in the hospital. In general, these sixty-three children have not as a group been malnourished, anemic, or easily fatigued.

Eight other children have been included in this group as having complaints unexplained by examination except as they might be related to the presence of such glands. Their symptoms form a miscellaneous collection which may be summarized briefly as follows: Two children had low back pain of one and five years' duration; one had weight loss and urinary frequency (for two months); one had urinary frequency and slight fever (for one month); one hematuria (five attacks in two years); one anorexia, nausea, and diarrhea (for two months); and in two there were malnutrition, nausea, and night sweats for one and two years.

In those children whose symptoms were of a general nature, as in the last three mentioned, it is possible that the calcified glands were part of a tuberculous process still active enough to disturb general health and perhaps not entirely localized in the abdomen, though examinations of other parts of the body were negative. As in all of the children with miscellaneous symptoms, no other diagnosis could be made, and the symptoms have cleared under moderate rest and good hygiene.

In the others, we cannot prove any mechanical relationship between the presence of calcified abdominal glands and such varied complaints as back pain, hematuria, and urinary frequency. It is quite possible that no such relationship existed. Back pain has not been mentioned in the literature except as pain may be referred to the back from the abdomen. Many authors, notably Thomson-Walker,10 have thought that calcified glands might cause hematuria and other urinary disturbances. Their evidence has been criticized by Strömbeck.<sup>8</sup> In our patient with hematuria, pyelograms did not demonstrate a topographic relationship between the glands and the ureters or kidneys, and the urine was negative for significant organisms on culture and inoculation. One child with urinary frequency had a negative cystogram and a bacteriologically The other cleared up before complete studies were negative urine. made. All the children with urinary symptoms recovered without special therapy, and in none have later disturbances or findings indicated a different diagnosis.

# ETIOLOGY OF PAIN

Since the most consistent symptom accompanying the presence of calcified glands is abdominal pain, considerable speculation has arisen as to the manner of its production. The subject has been reviewed re-Golden and Reeves<sup>2</sup> and Auchineloss<sup>3</sup> discuss the cently by Mead.11 usual theories. Most explanations are based upon peritoneal irritation, either inflammatory or mechanical; mechanical irritation of sympathetic nerves; the associated presences of adhesions, bands, and contractures, as well as possible active intestinal or mesenteric lesions; and finally damage to the lymphatic or vascular drainage of a part of the intestine, with the substitution of a makeshift, compensatory mechanism. Auchincloss mentions the possible rekindling of allergic areas in these nodes by reinfection of a tuberculous nature. Attempts have been made in nineteen of our patients to determine the cause of pain by gastrointestinal barium series. In sixteen the findings were negative; in two there was some visceroptosis; and in one a hypermotility was found. same child had a negative series a year later, when she was still having symptoms.

Our material offers two fairly large and fairly equal groups of cases, one with definite abdominal pain and one without symptoms. We have reviewed the available roentgenograms in these two groups in an attempt to learn whether any particular size, degree of calcification, site, or number of calcified glands is particularly likely to be associated with pain. The results are analyzed in Table II. It is to be noted that the percentages show no very consistent or illuminating differences. They indicate no type of calcified gland or glands in which one might predict the likelihood of present or future pain, nor are they helpful in explaining the manner of pain production. That pain actually is associated with their presence, we have no doubt.

One finding of interest in the review of these 123 roentgenograms was the occasional presence of calcification very low in the pelvis. Since the glands usually involved are in the mesentery, shadows may appear almost anywhere in the abdomen, or even in the upper pelvis; but in films from four children they appear at the level of the fifth sacral vertebra, and in one other child (Fig. 1), a calcified area was noted at the level of the coccyx. It is true that the technic of taking abdominal roentgenograms tends to make objects in this region appear lower than they actually are, but such very low shadows suggest a calcification of the iliac group of glands. We have no proof that such is the ease in these patients. If these glands actually were involved, it must mean that in these five children, all of whom were girls, tubercle bacilli must have reached these glands from the pelvic peritoneum, uterus, or tubes.

#### PHYSICAL FINDINGS

An attempt has also been made, so far as the data are available, to correlate the symptoms and physical findings, particularly pain and tenderness, with the location of the glands as determined by roentgenograms. Of fifty-two cases in which data as to pain were available, it was diffuse throughout the abdomen in twenty-three; it coincided with the location of the glands in sixteen; and it disagreed with the roentgenogram as to side or level in thirteen. Of thirty-one cases in which tenderness was recorded as demonstrable, the tenderness was diffuse in three, coincided with the x-ray findings in fifteen, and disagreed with the x-ray findings in thirteen. It was pointed out by Floderus12 in 1910 and reiterated by Head13 in 1926 that tumor is a relatively constant finding. In only four of our cases was there a palpable mass noted; in all it coincided with the roentgenologic picture. This discrepancy might be explained by the fact that all of our cases were of children in whom the process had not sufficiently advanced to cause the large masses palpated by former writers. However, in those patients whom we have followed into their late teens, we still fail to find the tumor by careful palpation, even with the help of the roentgenogram. Of the twentyseven patients whose pain is recorded as localized, it was right-sided in eleven, but located in the right lower quadrant in only four. Pain was present on the left side in nine, and localized at the umbilious in five.

Tenderness has often been described as a common physical finding, especially tenderness in the right lower quadrant, and it has been pointed out by several writers, 1, 11-14 that the tenderness of such glands differs from that of appendicitis in being somewhat medial to and above Mc-Burney's point, corresponding anatomically to the position of the glands in the ileocecal mesentery. Of the thirty-one cases with recorded tenderness, fifteen were localized in the right lower quadrant, but no exact point of maximum tenderness could be made out. Also, in several of these fifteen cases, the glands were found by x-ray to be on the left side of the midline. Our findings are in agreement with those of other writers in that we are able to demonstrate no exact clinical picture for the majority of these patients.

#### TREATMENT

Before discussing our experiences with the management of this condition, it should be repeated that we have tried so far as possible to limit this study to children with glands which have calcified and are presumably not in an active state of tuberculous disease. It is for this reason that we have refrained from considering the symptoms and outcome in the seven children who had an associated tuberculous peritonitis. In them an active or subsiding disease process might invalidate conclusions concerning the glands themselves. That the calcification of glands may not always be a guarantee of the quiescence of the process is shown by one instance described below. However, when repeated roentgenograms have been taken during the months or years following the discovery of the first calcium in our patients, new shadows have not appeared on the plates. Thus, the symptoms would appear to be asso-

ciated usually with lesions already calcified, rather than with any associated active inflammation.

Some writers have not made this distinction clear, and a resultant confusion clouds the appraisal of measures proposed for therapy. Patients such as ours, with calcified glands have been referred to in the literature as having "surgical tuberculosis," thereby giving the impression that surgical treatment is of necessity indicated. This impression is strengthened further by repeated statements that exploration of the abdomen is always indicated when symptoms are acute. Some writers appear to advise laparotomy even in the presence of mild symptoms, defending the procedure as a diagnostic aid. We feel that this is unjustified, except in cases in which it may be thought wise to determine the presence and degree of a suspected associated active tuberculous process.

Obviously, in those cases with abdominal pain and tenderness in the proper region, appendicitis must always be considered. In some instances appendicitis has been present in a child whose flat plate showed calcified glands, or the picture may be so confusing that it cannot be clarified without laparotomy. This occurred in the only one of our patients in whom surgical exploration showed a possibly active tuberculous process associated with calcification.

CASE 4 .-- A. L., a boy aged five years, had had pains about the umbilieus at monthly intervals for eighteen months. There was occasional vomiting. was no history of tuberculosis contact, but he had received raw milk during his first year. The tuberculin test was positive; no chest x-rays were taken, but those of the abdomen showed a mass of calcified glands just to the left of the midlumbar region. Examination of the abdomen was entirely negative though he had complained of pains the previous day. Two months later he was found to have some tenderness and slight spasm in the right lower quadrant. Although his pains were not increasing and his condition not acute, it was decided to remove the appendix and investigate the glands. At laparotomy a large mass of glands was found in the mesentery of the ileum, one of which was broken down and showed yellow through the thin covering over it. An attempt was made to enucleate this gland with removal of caseous material and some lime salts. The cavity was sterilized with iodine. A few adhesions which were drawing the bowel toward the mass of inflamed glands were divided. The appendix did not appear grossly pathologic to the operator but was reported by the pathologist as showing an acute appendicitis and as containing several thread worms (oxyuris). Unfortunately no pathologic study of the glandular material was made. Convalescence was uneventful. In the five years since the operation the child has been well except for very mild and transient abdominal discomfort occurring at intervals of two or three months.

Here the presence of caseation may indicate some activity of the tuberculous process. It is, of course, impossible to neglect the appendix as a cause of his symptoms, but the history of pain in the umbilical region for more than a year points to the mesenteric glandular process as a very probable background. The case illustrates that exploration

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may sometimes demonstrate glandular lesions which have not yet become entirely quiescent.

Surgical manipulation of tuberculous processes not completely inactive may involve some risk to the patient. Our follow-up of children whose symptoms were treated purely expectantly indicates that this risk need seldom be taken (Chart 1). There is, however, a more definite indication for surgery in children in whom intermittent and severe abdominal pains persist or increase during years of treatment by modified rest and hygiene. When this happens, one need have little fear of encountering an active process, so that the widespread excision of as many nodes as possible may be indicated. The good results following such an operation have been stressed particularly by Auchineloss.3 In only three of our seventy-one children with symptoms has this operation These cases are abstracted below: In the first two seemed advisable. cases (Cases 5 and 6), such an excision was performed with very definite relief; in the third (Case 7), we feel that the course of events practically demands it.

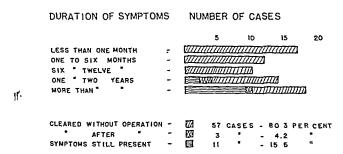


Chart 1.—Duration and outcome of symptoms in seventy-one children with calcified abdominal glands.

CASE 5.—J. J., an eleven-year-old girl, was first admitted to the surgical service of the Children's Hospital in August, 1934, with a history of vague right lower quadrant pain of one year's duration. There had been one acute attack of pain and vomiting. Roentgenograms eight months before admission had shown several calcified mesenteric glands (Fig. 5). Because her pain had been increasing to the point of making her life miserable, operation was finally decided upon. Laparotomy with appendectomy and excision of only one node in the ileocecal mesentery was done. The patient showed recurrence of symptoms following operation even under a rest regime, and was readmitted in October, 1934, when several more nodes, lying deeper in the mesentery, two of which were calcified, were removed. At no time after the second operation did the patient complain of abdominal pain. She was discharged home on the eleventh postoperative day; roentgenograms taken one month after operation revealed no calcified glands remaining. At the present time, six months after operation, she is in good health, is gaining weight, and has no pain or discomfort.

Case 6.—L. M., a girl of nearly nine years, was sent to the hospital from another state because of recurring abdominal pains of three and a half-years' duration. Her family and dietary histories were negative. At her first attack

of pun, an appendix, described by her home physician as "not acutely red and without definite absects formation," had been removed. She was then five years cld. Nine months later she had a tew days of pain, sweating, and pallor, and attacks of this nature recuired from six to ten times yearly thereafter. Examination at admission showed only some deep tenderness in the right lower abdomen Tuberculin was positive. There was some pus in the urine, which cleared in three days. Pyclograms showed normal kidneys and uncters but a mass of irregularly



Fig. 5—Case 5 in text. Several calculed glands in front and to right of second and third lumbar vertebrie Abdominal pain not relieved until all calcified nodes were surgically removed.

calcified glands in the right lower quadrant. Chest films were not taken. Because of the prolonged history without amelioration of symptoms, laparotomy was performed. Adhesions about the appendectomy stump were freed. Six irregularly calcified glands in the ileocecal mesentery were removed. Inoculation of material from these nodes into a guine i pig did not produce tuberculosis. The child has hid no pain or other symptoms in the three months which have elapsed since the operation.

CASE 7.—M. P., a five-and-one-half-year-old girl, was admitted to the hospital in October, 1930, because of intermittent fever, night sweats of three months' duration, and a nonspecific skin rash. Three days before entry she had watery stools. Examination was essentially negative, and laboratory studies revealed no active tuberculosis. A tuberculin test was positive, and roentgenograms of the abdomen showed three calcified mesenteric glands (Fig. 6). She remained in the ward sixteen days, running a nearly normal course and gaining 3 pounds in weight. She was then sent to the convalescent home, where she remained under strict supervision for one month. In over four years of good home care since then, she has had attacks of fever (supposedly to 102° F.) every three or four months, lasting from one day to two weeks. She has had pains in the abdomen every four or five days during this period of years, occasionally sufficiently severe to cause her to cry out. The pains have been confined to the left upper quadrant. Exami-



Fig. 6.—Case 7 in text. Calcified glands in the left upper abdomen of a girl aged five years. Pains increasing during four years of modified rest. Definite tenderness over glands. Surgery advised.

nation at the present time reveals definite tenderness in the left upper quadrant. While no masses can be felt, repeated x-ray plates show the same calcified nodes coinciding exactly with the area of pain and tenderness. It is planned to advise removal of these nodes.

We wish to stress several points of importance in these two cases. First, the fact that only three patients have been considered as subjects for complete excision of calcified nodes indicates our feeling that conservative management should first be given a prolonged trial and will in the great majority of cases be successful. Second, as shown by Cases 5 and 6, complete excision of involved nodes can definitely bring rapid relief for prolonged pain from this cause. Third, as in Case 7, one

should insist on the failure of other measures before resorting to surgery. If pain and tenderness are demonstrable in the region of the glands, operation may be more strongly urged. An overemphasis upon operation for this condition has perhaps developed from the many reports in the literature in which inferences are drawn from one or two cases operated upon early, sometimes before a flat plate of the abdomen had been utilized to indicate the diagnosis. The possible complications, usually referred to in the literature, are ileus, perforation, abscess, pressure on other organs, and miliary tuberculosis. Hemorrhage and mesenteric thrombosis are also mentioned. Hydronephrosis as a rare complication has been described. We have found none of these conditions. The size of our group would lead us to think that any dangerous complications, once the glands have reached the stage of calcification, are rare enough so that we feel no apprehension over a conservative policy.

No precise routine of nonsurgical management can be outlined. We have advised a good diet containing pasteurized or boiled milk and adequate vitamins, exposure to the sun, and above all, that amount of daily rest which seems to induce the cessation of pain. This may mean anything from a month or more in bed to half an hour's rest after meals. It is usually surprising what a very little rest will do for these children. Chart 1 has been constructed to demonstrate graphically the outcome of symptoms in the seventy-one children whose data are presented in Table IV. It shows that in slightly over 80 per cent of the group the complaints have cleared under such symptomatic therapy. In three patients, as mentioned above, operation has been performed with entirely satisfactory results. The remaining eleven patients (15.5 per cent of the group) report symptoms of varying severity to be still present. These symptoms are for the most part of long standing, having been present more than five years in the majority of the eleven. Without a detailed analysis of these children, it may be stated that in eight of them the attacks are mild and infrequent; in one the evidence of actual pain is uncertain and indefinite; and in only two do symptoms seem to interfere with the well-being of the patient. In the one of them who is still within the age limit of our clinic (Case 7) operation is being advised.

#### CONCLUSIONS

1. A study has been made of 147 children with calcified abdominal lymph nodes, seen at the Children's Hospital during the past ten years.

2. The relation of this finding to tuberculosis in general is discussed. The evidence points to the ingestion of tubercle bacilli, probably from infected milk, as being the usual cause of calcified abdominal glands. Such glands apparently are not important foci for the dissemination of tuberculosis to other parts of the body. Active pulmonary tuberculosis did not develop in the later course of any patients. Associated tuber-

culous lesions were more commonly nonpulmonary than pulmonary. Two children died of tuberculous meningitis, but this was not definitely due to dissemination from the abdominal glands.

- 3. About half of the total group had no symptoms referable to the glands. In the remainder the usual symptom was prolonged and recurrent abdominal pain. In a few other children there were miscellaneous symptoms unexplained except by the presence of the calcified glands. Physical examination presented no characteristic picture.
- 4. A review of the roentgenograms in the children with and without abdominal pain has shown no particular size, location, degree of calcification, or number of such glands, to be characteristic for the production of pain.
- 5. In a few female children the presence of calcified glands very low in the pelvis suggests the possibility of their infection from the pelvic peritoneum or the genital organs.
- 6. Treatment may be symptomatic with moderate rest and attention to diet and hygiene, or it may be surgical, either with exploration or with complete excision of the glands in cases refractory to symptomatic treatment.
- 7. In sixty-nine children without local symptoms no treatment was usually advocated beyond safeguarding the milk supply. The outcome in this group has been satisfactory except for the two children with meningeal involvement. Of seventy-one children with symptoms, fiftyseven (80.3 per cent) have recovered under general hygienic treatment: eleven (15.5 per cent) still have some pain; and three (4.2 per cent) have been treated surgically with relief. Surgery at present seems indicated in one other child whose pain is increasing under nonsurgical management. Surgery seems to us advisable and most successful only after the prolonged trial of general symptomatic measures.

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#### AN ESSAY ON THE RATTLES

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SUDDEN attack of laryngeal obstruction accompanied by loud, A SUDDEN attack of laryngear obstruction according harsh stridulous breathing, rapidly increasing and continued respiratory difficulty, and an anxious facial expression is, in the lay mind, one of the most alarming of childhood diseases. It almost always causes considerable apprehension and leaves an indelible impression on the parents, and even physicians, more intent upon differential diagnosis and effective treatment, are seldom able to regard it with absolute composure. In biblical times, the progressive suffocation from complete larvngeal obstruction was considered the most terrible and painful of the 903 known causes of death; and the Emperor Napoleon, although accustomed to the suffering and slaughter of wars, was so moved at the death of his nephew, his contemplated successor, that he offered a prize for the medical solution of the problem. The clinical picture of laryngeal obstruction has been repeatedly observed throughout the ages and frequent references in both lay and medical literature can be found, but there is probably no medical condition to which so many descriptive but unrelated terms have been applied. It is to this constantly changing terminology that I wish to call attention and incidentally to show that in former days a superficial resemblance of signs and symptoms caused many unrelated conditions to be considered as one disease.

About a century ago, John Redman Coxe, a Philadelphia physician, scarched the early medical literature to find if the ancients were familiar with the syndrome, and he thought that under the words "dyspnea" and "asthma," depending upon the degree of obstruction, he could discern some cases of the disease. Though today asthma has a very special meaning, it was not so very long ago that this word was used for laryngeal conditions. Underwood, for instance, has a chapter on the "asthma infantum spasmodicum" which was synonymous at that time with the croup or acute asthma.

One of the most popular names for a very long time was the Latin word cynanche (pronounced sin ann' ki) which was derived from the Greek κίων, dog. and άγχαν, to choke or strangle. How strangling came to be associated with a dog I do not know. One writer suggests that this name was selected because dogs and wolves were supposed to suffer from the same disease, and another that the choking suggested a dog's collar, but perhaps the harsh, hollow cough that often accompanies laryngeal conditions suggested the barking of a dog. At any rate, "cynanche" was used for years and was a very old term

even in 1662 when the Connecticut General Assembly declared a day of thanksgiving for deliverance from an epidemic of cynanche trachealis, in this instance probably laryngeal diphtheria.

In many of the older texts it is very difficult to know whether the author is referring to diseases of the throat or to diseases of the larynx. Aretæus (third century) used κυτάγχη (cynanche) when there was inflammatory swelling and συτάγχη (synanche) when there was a narrowing or constriction of the parts, but Paulus Æginata (seventh century) used "cynanche" for inflammations of the trachea and "synanche" for inflammations of the throat. Others used the words interchangeably, and as a result of the confusion we find the word "squinancy." There is a black letter work by John Vigo, for instance, printed in 1586, with a chapter, "Of an Apostume of the Throte called Squinantia." In place of "squinancy" we sometimes find the contracted forms "squinacy." "squinsey," and "quinsey." Although nowadays "quinsy" is used solely for peritonsillar abscess, for a long time it meant laryngeal obstruction. Here is a quotation from Thomas Phayre (1544) on "this outragious sickenes":

#### OF QUINSEYE AND SWELLING OF THE THROTE

The quinsy is a daugerous sicknes both in young & olde, called in latin angina,\* it is an inflammacion of the necke with swellyng and greate peyne, sometime it lyeth in the verye throte, upon the wesaunt† pype, and then it is exceeding perillous for it stoppeth the breath, & stranguleth the pacient anone.

Other whyles it breaketh out like a bonche on the syde of the necke, and than also with verye great dyffycultye of breathynge, but it choketh not so sone as the fyrst doeth, and it is more obediente to receive curacion.

The signes are apparaunt to syghte, & besides that the chylde can not crye, neyther swallow downe his meat and drynke without payne.

Although the old New England quinsey of the seventeenth century may have been any laryngeal or pharyngeal condition, there can be no doubt about the quinsy of 1740, as described by the Rev. Jonathan Dickinson, founder of the College of New Jersey (Princeton) and, by the way, an excellent physician:

This Disease appears sometimes in the Form of a Quinsey. The lungs are inflamed, the Throat and especially the Epiglottis exceedingly tumefied. In a few Hours the Sick is brought to the Height of an Orthopnoea; and cannot breathe but in an erect Posture, and then with great Difficulty and Noise. This may be distinguished from an Angina by the Crustula in the Throat, which determines it to be

<sup>\*</sup>Angina, like quinsy, in the old days, was applied more to laryngeal than to both words have the root "AGH" or its nasalized form angere, to choke; Sanskrit, amhas, pain. The words anger, anguish, anxious, angina, auce, and uply have this common root.

twesaunt, weasand, etc. Literally "the wheezing thing." The word generally stood for trachea but was also frequently used for larynx, pharynx, or esophagus. "But monie daily weet their weason wi' liquors nice,"—Robert Burns (1785). Our slang "wet your whistle" may possibly have a venerable ancestry.

a Sprout from the same Root with the Symptoms described above. In this Case the Patient sometimes dies in twenty-four hours. I have not seen any one survive the third day.

Laryngeal diphtheria is sometimes very difficult to distinguish from acute catarrhal laryngitis, and the early writers undoubtedly thought that they were different degrees of the same disease because the same or similar terms were often used to describe them both. In the following anecdote.<sup>2</sup> the repeated attacks, each followed by recovery, make catarrhal laryngitis the most likely diagnosis:

Aug' 11th or thereabouts, 1730. My Eldest son, Samuel, swallow'd a Brass Pin, reather better yn an Inch & half long, wth came thro' Him in abt 44 Hours—a wonderfull salvation, may G<sup>d</sup> have ye glory of it. & if my Child lives to take Notice of this Record, he Quickened ythy to Devote himself to G<sup>d</sup> who wonderfully appear'd for Him in ye Deliverance, as well as many times heretofore wn He has been brought very low with ye Squinancy.

"Canker" was occasionally used for laryngeal obstruction as in John Walton's account below, but generally it meant the same as our exudate or membrane in the throat. It (cancer and chancre also) came from the Latin cancer, erab, and one has a choice of many ex-In discussing cancer, Paulus Æginata said, "The veins are filled and stretched like the feet of the animal called cancer, and hence the disease has got its appellation. But some say that it is so called because it adheres to any part which it seizes upon in an obstinate manner like the crab." In his chapter "Of a Canker in the Mouthe." Thomas Phayre wrote: "It is so named by reason of crepynge and catynge forwarde and backewarde, and spreadeth it selfe abrode, lyke the feete of a creues, called in latine cancer, notwithstanding I knowe that the Greekes, and auncient latvnes. gyve other names unto thys dysease, as in callynge it an ulcer, other whyles aphthe, nome, carcinomata, and lyke, which are al in englyshe. knowen by the name of canker in the mouth. . . . "

There was a time, particularly in eighteenth-century America, when epidemics of diphtheria and searlet fever frequently occurred together, and for many years the two diseases were hopelessly confused because it was believed that both diseases were caused by the same "morbifick matter" in the blood and had different appearances depending upon whether this "morbifick matter" settled on the skin or in the throat. At that time, "canker" was diphtheria and "canker rash" was scarlet fever but during the epidemics many laryngeal cases were seen and then we find the condition described as "canker quinsey." This is said to have caused the deaths of the eight children of Mark How. of Ipswich, all of whom died between Nov. 5 and Nov. 28, 1735. A similar diagnosis is found in the Wintonbury (Bloomfield) church records:

Pamela, child of Russel Manley. Jan' 28th [1800], aged 21/2 years. Horse canker.

(In other words, hoarseness, indicating laryngeal involvement, superimposed upon an ulcerated throat.)

Perhaps the quaintest and most descriptive of the purely American terms was "bladders in the windpipe." If "bladders" was used to mean something that could be quickly distended by air or water, perhaps, after all, the analogy was not far-fetched when we recall the edema that often accompanies inflammation. It is doubtful if the old Puritan doctors had any such thoughts in mind, nevertheless the phrase was frequently used for laryngeal obstruction, in the following quotation again for the diphtheritic kind:

In December, 1659, the (until then unknown) Malady of Bladders in the Windpipe, invaded and removed many Children; by Opening of one of them the Malady and Remedy (too late for many) were discovered. Among those that thereby expired, were the Three Children of the Reverend Mr. Samuel Danforth. . .

Closely akin was the descriptive "rattles in the throat," and among the deaths in the West Hartford church records there is reported:

Jan 29th 1765. Abraham (son of Abrahm) Sedgwick. Obstruction of the Lungs vulg. dict. Rattles. 6 yrs.-8 mos.

Of some interest in connection with the word "rattles" is an early American medical work published in Boston in 1732 and to which very little attention has been paid, and rightly so, for it contains very little of scientific interest and certainly no notable descriptions. Perhaps its rareness may be the reason for its neglect. It is worthy of some attention, however, chiefly because of its quaint pathologic descriptions, its presumptive evidence that diphtheria was common in New England, and because it is probably the first medical work by a graduate of Yale. But first a word about the author.

John Walton (1694-1764), a native of Preston, Conn., was graduated from Yale in 1720, where he had been an industrious student with a bent for serious poetry. He became a Presbyterian minister and preached at Crosswicks, Allentown, and Cranberry, in New Jersey where "his preaching was admired. People heard him with many tears." But evidently his religious principles had little influence on his own way of life, and in the spring of 1722 he was suspended by the Presbytery of Maidenhead "for his lustful carriage to some young women." Walton continued to preach, however, and was formally suspended a second time but he appealed to the Synod, and it was agreed that he could continue preaching provided he would confess. The confession was such that the other ministers who heard it "were surprised." On account of "further contemptuous behaviour" he was suspended for good in October, 1723.

He is then thought to have opened a private school in New York City where he advertised for pupils in Hebrew, Latin, and Greek; but the desire to be a minister again overtook him, and he next appears in charge of the Presbyterian churches in White Plains and Rye, New York. Eloquent and persuasive, he was able to stir up considerable religious strife, and about this time (1728) the rector of the neighboring Episcopal church complained that "this Walton, being a bold, noisy fellow, of a voluble tongue, drew the greatest part of the town after him," and the Congregational ministers warned all others to beware. Yale College twice refused him the degree of Master of Arts.

When we next hear of Walton he is a farmer as well as a minister, preaching and writing in defense of the Baptist faith and soon thereafter he was recommended by the Governor of Rhode Island to be the minister of the First Baptist Church in Providence. Not receiving the appointment, he gave up the ministry and went into law and politics. In October, 1733, he was admitted a freeman of the colony and in 1743 represented Glocester in the General Assembly. The last we read, he is an Associate Justice of the Rhode Island Supreme Court.

In those days it was not unusual for ministers to heal the bodies as well as save the souls, and it is said that Walton practiced medicine while living in the vicinity of Providence. It was during this brief interlude in his varied career that. I presume, he wrote "A Short Essay on Rattles and Canker." which, although it has a separate title page, was printed and bound as a part of An Essay on Fevers, the Rattles, & Canker. The paragraph concerning the pathology of respiratory obstruction is quaint enough:

If we consider the Frame of our Bodies, we shall find they consist of Solids and Fluids; and when any of these are raised above or depressed beneath the Ballance of Nature, that then Health will be annoy'd, and various uneasy Symptoms ensue. So in the Case now to be explained, we may justly conclude, that there are some disagreeable Particles that affect the Lungs and Throat, and hinder the regular Circulation of the Fluids, and destroy the Solids; and that these proceed from an Error in some of the Non-naturals, especially the Air, which (as the excellent Sydenham has prov'd) contains the Seeds of the most Epidemical Diseases. Now whilst the Air or Breath passes into the minute Branches of the Wind-pipe, and as the Blood circulates through the Lungs, in Channels that accompany the Tubuli of the Trachea, if either or both of these contain heterogenous Particles that stick in the Lungs, especially if they fill up the small Branches of the Wind pipe, the Air will soon be obstructed from impregnating the Blood with those Particles that give it a Momentum, and keep it from cohering in too bulky Globules; upon which there will ensue Obstructions of the Circulation of the Blood in the Capillary Branches of the Pulmonary Artery and Vein, and the Breath be gradually excluded from entring the Lungs, which must necessarily occasion a Difficulty of breathing, an Inflammation and Fever, and sometimes erosions of the Solids. And according as the Morbifick Particles are shaped, and the place they settle on, so we distinguish the Distemper. If they are very sharp pointed and large, so as to corrode the Solids when crouded against them by the Air on one side in the Trachea, or by the Blood on the other side, or otherways, then we call it the Canker; but if they are Spharoidal, Conical or Cubical, &c. we distinguish them according to their Figures, Cohesions, Bulks, Motions, and Effects consequent thereupon: load of these lie long upon the Lungs, there will be a Consumption, and Ulcers

breed accordingly, and a Hectick ensue. And in ease the Obstruction be sudden, great, and principally in the fine Branches of the Wind pipe, and the Farticles not much pointed, but cohere so as to constitute what we call Tough Phlegm, then 'tis that which we call the Rattles, or Quinsey in the Lungs, especially in Children; and is distinguished according to the Nature and Quantity of the Phlegm, and the Noise the Air makes when it endeavors to inflate the Lungs, and the Difficulty in Breathing. But in case the Obstructions seize the Lungs near the Mouth, 'tis called a Quinsey. Here it must be observed, that these Obstructions are extensive; for as the Blood swiftly circulates through all parts of the Body, it absorbs some of the Morbifick Particles, and conveys them to different parts of the Body, and dischargeth them in every convenient place, especially where the Glands are most open: Hence the Salival Glands are so often affected, especially with the Cankery Particles, and Scurry Scropholous Tumours.

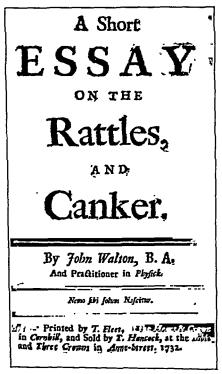


Fig. 1.

If John Walton had followed Sydenham's teachings more carefully and recorded simple facts instead of the iatromathematical theories of an earlier day his essay might have been more important and he would not have been so far behind the times. As an example of what he might have done, there are extracts from the diary of Samuel Sewall, Jr., written at nearly the same time and containing a few simple bedside observations. Although unrecognized, it is probably the first written account, in America at least, of what used to be a very common disorder. The patient, John Sewall, was the great-

grandson of John Hull, the mintmaster, of Pine Tree Shilling fame and the grandson of Chief Justice Samuel Sewall, the noted diarist. John Sewall was the sixth child and about nine months old when his troubles began:

1724. Jan 3. In the Night son John have two short fitts. 4th. Wife goe to see him.... 12th. In the Night son John have a fit. 14th. Towards morning he has another short fit. 15th. Send Mathew for son John. His Nurse Sarein comes with him. Next day goe home. Her sister Lydia comes to assist in weaning him.... Feb. 2. Son John have a short Fit.... 17th. Son John, about six a clock, have a convulsive fitt. Held him rather better than a qu. of an hour.... March 10. Something before day, son John have a fit & by 7 morn, have six. Noon, one a longer & stronger. Send for Dr. Tompson. Mathew see him by Sharps & he came. Look'd upon the Child & saies he has a bladder in his throat.... April 20th, very hot. Carry John with Nuss Lee to Widow Ruggles (alias Fiedler) for Her to keep him.... Aug. 18th. Mrs. Ruggles send her Daughter to acquaint us that son John had a Flux & vomited. As we went to Boston called & see it, it being considerably ill. As we goe to Boston call at Dr. Tompsons. He gone to Boston. Call as we come Back & take him with us. We thought he was better, and so went home.

By a "bladder in his throat," Dr. Tompson undoubtedly meant a laryngeal obstruction and so we have an explanation of young Johnny Sewall's complaints. His age, the season, repeated convulsions, laryngeal "crow" and ultimate recovery give us a diagnosis of tetany, or for those who prefer what has been called "the somewhat pedantic and cacophonous title—Laryngismus Stridulus."

The scrunke or askara of the Talmud, the garrotillo of seventeenthcentury Spain, paedanchone (child-throttling), and morbus strangulatorius were sometimes used, but there still remain a few other terms about which I would like to say a word. In early English medical literature many diseases characterized by difficult breathing were called "the rising of the lights," the "lights," or lungs, being distinguished from the other organs by their weight. Later, especially in the north of England, laryngeal obstruction was commonly called "chock" and "stuffing," the reason not difficult to imagine, but why it was called "the great hives" in Ireland and Scotland is beyond my ken. In colonial Pennsylvania and New Jersey, it was also called the "hives," which, according to Benjamin Rush, "appears to be a corruption of the word 'heaves,' which took its rise from the manner in which the lungs heave in respiration. The worst degrees of the disorder are called 'the bowel hives,' from the great motion of the abdominal muscles in respiration." There seems to be some discrepancy here, for "bowel hives." as distinguished from "chest hives," was also used to describe intestinal disorders, rickets, skin diseases, and various other things (Still).

<sup>\*</sup>Morristown, N. J., Bills of Mortality April 24, 1774. Nathan, son of Peter Nor-ris, jun, act. 2, Hives.

The word "croup," the most popular name today and the one which seems likely to survive, goes back to the Anglo-Saxon but came to us as a medical term from Scotland, where it was applied to various forms of laryngitis supposedly because of a similar disease—the croup or pip-of poultry. It was introduced into medical literature by Patrick Blair in 1718:

The Tussis Convulsiva or Chink-cough, is also some Years Epidemical, and becomes universal among Children; as is a certain Distemper with us, called the Croops, with this variety, that whereas the Chink-cough encreases gradually, is of a long continuance, seizes in Faroxysmes, and the Patient is well in the Interval. Convulsion of the Larinx as it begins so it continues, so violently, that unless the Child be relieved in a few Hours, 'tis carried off within twenty four, or at most forty eight Hours. When they are seized, they have a terrible Snorting at the Nose. and squeeking in the Throat, without the least Minute of free Breathing, and that all of a sudden, when perhaps the Child was but a little time before healthful and well.

Francis Home, another Scotch physician, wrote a pamphlet on the disease (1765) and I can think of nothing more appropriate to bring this discussion to a close than some comments on Home's work which were written by Dr. Buchan, a well-known eighteenth-century pediatrician. He writes from Sheffield, England, to his friend William Smellie, a printer in Edinburgh:

I cannot make out from your account whether Dr. Humes pamphlet on the Croup is wrote in Latin or English. If in the former, I think Suffocatio Stridula a very proper name; but if he translates that into Croup, he may keep his pamphlet at home; for I have never met with any man in England, either medical people or others, who called the disease by that name. Though that disorder is very common here, yet should one speak of the croup to a Yorkshire man, he would believe you either meant the rump of a fowl, or the buttocks of a horse. The disease, however, is by no means sufficiently understood; and I should be extremely glad to be possessed of any good performance on the subject. Betwixt you and I, it does not matter a pin what name any man gives a disorder, provided he points out the symptoms accurately, and proposes a rational method of cure.

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### Critical Review

#### THERAPEUTIC USE OF DIETS

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THE custom of the past in prescribing diets for those who were ill I was to specify the exclusion of certain types of foods which were considered undesirable because of the nature of the patient's illness.1 A more positive approach to the problem is to prescribe certain specified foods which are needed by the body for the maintenance of normal nutrition in health or in illness, then to adapt the nature of the prescribed foodstuffs to meet the requirements peculiar to the patient's condition. The growing recognition2 of disease states brought about by deficiency of the diet in certain essentials for normal nutrition has led to the adoption of this second approach to diet control as being much safer for the patient and much more effective therapeutically. Evidence is rapidly accumulating to show that attention should be paid to the completeness of the diet of the individual who is not ill so that disease may be avoided and that optimum levels of health may be approached. The needs of the patient with any type of illness are qualitatively similar to those during health, and equal attention should be directed toward meeting them. The weakness, anorexia, or incapacity of the patient makes it imperative that the attendants maintain the initiative in supplying food of a thoroughly suitable nature for the patient. The first consideration in designing a dietary program for a patient with any type of illness should be the completeness of the diet in all recognized essentials of nutrition, with liberal rather than minimal amounts of the protective dietary substances. ture and amount of the foodstuffs may be determined to meet the peculiar conditions imposed by the nature and degree of the patient's illness, but valueless restrictions should not be imposed. words, the diet prescription should be one of inclusion rather than exclusion, restrictions always being accompanied by advice as to the inclusion in the diet of substitutes which nutritionally are equivalent to the prohibited foods. Unless such a policy is pursued, a prescribed diet of limitation may be a source of danger and of damage rather than of benefits to the patient, and the induced disturbance of nutrition may more than offset the therapeutic value of the restriction. In all instances, the patient rather than his disease should be treated.

For convenience in discussion, therapeutic dicteties may be considered under the following categories:

- Diet in acute or chronic illness in which the nature of the disease does not of itself predicate the types of foods which may be used.
- 2. Diet in conditions in which the patient's ability to digest or assimilate foodstuffs is impaired.

- 3. Diets for those with allergic states.
- 4. Diets designed to correct specific or nonspecific deficiency states.
- 5. Diets designed to alter the acid-base balance of the tissues.
- 6. Diets for the control of diabetes mellitus and other disturbances of metabolism.
- 7. Diets designed to conserve the excretory functions.

Preliminary to the discussion of types of diet management best adapted to each of the above conditions, it is well to review the characteristics of a desirable diet for the healthy individual since the therapeutic diet will be based on a similar regimen so far as possible. Clinical and metabolic studies have indicated that diets of a high protective content offer the individual definite advantages over the type of diets customarily offered in homes and commercial eating establishments. As a guide in designing the diet of a healthy child of school age, the following ingredients have been specified as a desirable basic daily intake, these foods to be supplemented but not replaced by foodstuffs which may have a lower protective power, but which offer attractive or economically desirable sources of energy:

1 quart of milk

1 or 2 eggs

1 ounce of butter

1 teaspoonful cod liver oil

I orange, or tomato, or apple 1 additional serving of fruit

2 servings of vegetables, one of a fibrous nature

1 serving of meat, fowl, fish, or liver

While some of the essentials of the diet may be supplied equally well in the form of other foods, those listed are of a type readily available and of proved efficacy. Omissions are not to be made, unless the omitted foodstuff is replaced by another of comparable protective efficacy. In designing therapeutic diets, this list may be used as a guide, altering through suitable substitution in such a manner as the patient's age, physical condition, or disease may require. As an aid in making such an adaptation, it is well to consider each of the foods listed as to the reason for its inclusion in the list of requisites and as to the nature of permissible substitutions.<sup>5</sup>

Milk is the only practical food source of calcium. The normal child needs 11/2 pints of milk daily in order to meet adequately the calcium demands of his growing body. Equal amounts of skimmed milk or of buttermilk will supply similar amounts of calcium, as will 4 ounces of cheese. Oranges stand next in practicability as a source of calcium, but in this regard ten average sized oranges will be required as a substitute for a pint and a half of milk. The calcium content of other natural food products need not be ignored, but its concentration is so low that they do not represent suitable sources of importance. Calcium salts may be employed when milk cannot be taken in sufficient amounts; their utilization is less certain than that in milk, especially during illness and in the young child. Dicalcium phosphate seems to offer advantages over other calcium salts, particularly those which do not contain phosphate. A suitable daily dosage to meet the entire calcium requirement is 90 grains, or 6 grams. Because of its bulk, this is best incorporated in some semisolid food.

Milk is an important source of protein and when taken in the amount indicated will supply a good share of the body's needs in a desirable form. Suitable substitutes for this protein can be obtained from other sources of animal protein, such as meat products, in amounts greater than would be needed if milk were included in the diet. In the discussion of allergy, other milk substitutes will be named.

The vitamin B and G content of milk is noteworthy when the prescribed amount is ingested. When necessary to eliminate milk from the diet, increased servings of vegetables and of meat, especially liver, will help to complete the requirements for these vitamins. Foods made from seeds, such as whole grain products, peas and beans, also are valuable sources of vitamin B. The root vegetables are preferred to the leafy types as sources of vitamin G. Many of the so-called concentrates of these two vitamins are not appreciably richer in their content than are some of the common foods. Crystalline vitamin B has been produced and when commercially available may find a place of value in supplying that principle to those whose assimilative ability is so lowered that ordinary foodstuffs cannot be employed for the purpose.<sup>6</sup>

While whole milk, cream, and butter may constitute valuable sources of vitamin A, this property need not be stressed if the child is receiving cod liver oil in the amounts prescribed. Liberal servings of the pigmented vegetables also will forestall deficiency of vitamin A, if ingested and well utilized. Concentrates of vitamin A are available in the form of pro-vitamin carotene or the oil of halibut liver, and these may be employed if necessary to insure completeness of supply.

Cod liver oil offers a recognizedly adequate source of vitamin D; without the continuous use of it or of some equally potent source of the vitamin, there is the utmost likelihood of deficiency of vitamin D except in the individuals receiving considerable solar or other ultraviolet irradiation; the lack of clinical evidence of that deficiency does not negate its existence or its significance in the maintenance of the general level of health. With suitable amounts of vitamin D, as viosterol or as certain suitable concentrates of cod liver oil, the vitamin D requirement may be met as well as with cod liver oil. Unless properly fortified, however, these products may fail to insure adequacy of vitamin A intake. Moreover, they fail to supply significant amounts of iodine and of valuable fatty acids as contained in cod liver oil.

Fruits and vegetables supplement the mineral intake, provide bulk necessary for the regulation of intestinal elimination, and constitute important sources of vitamins A. B. C. and G. Because of the instability of vitamin C. it is well to include one raw vegetable or fruit in each day's food allowance; although orange or tomato is popularly specified for this purpose, most raw fruits or vegetables offer vitamin C in amounts sufficient for the body's needs, if suitable quantities are ingested. Acid fruits such as tomatoes retain much of the vitamin even after cooking. When therapeutic conditions make it necessary, vitamin C may be supplied as cevitamic acid. When roughage is contraindicated, juices from vegetables and fruits may be employed. A wide variety of fruits and vegetables usually is desirable, with emphasis being placed on the succulent types rather than those which are essentially of a starchy or seedy nature.

Eggs offer a desirable type of protein, together with other organic and inorganic substances of value to the rapidly growing animal organism. They do not seem to be essential foodstuffs but are valuable in their content of protective substances. Meat products and milk can be used to replace the protein they would supply; if cod liver oil is being taken as prescribed, the vitamin content of the egg will not be needed. With a liberal intake of iron-containing foods, such as liver and other meat products, leafy vegetables, or inorganic iron preparations, egg will not be needed for that purpose. The chief defense for including egg in the list of foods ordinarily prescribed lies in the fact that it is the foodstuff designed by Nature for the rapidly growing chicken from the earliest embryonic stage; it obviously is rich in the principles necessary for tissue growth, and possibly it furnishes important substances of a nature not yet recognized.

Meats are specified because of their content of proteins which are similar in their nature to those of the human body. During infancy the protein need can be met by sufficient amounts of milk, but thereafter the inclusion of meat is desirable. Meat also is a valuable source of iron and of vitamins B and G; the iron, however, is less available for human use than that from nonanimal sources. Liver is superior to lean meat in several respects and can be used advantageously at least once or twice weekly. Gelatin is not a satisfactory source of tissue-building protein; proteins from vegetable sources are less valuable for the body than those of animal origin.

#### DIET SUPERVISION DURING ILLNESS

The nutritive requirements of the body are not lessened by illness; on the contrary, certain food requirements are definitely increased when an individual is ill. The patient's nutritional state at the onset of illness will determine the urgency of his nutritional needs during a brief illness; if proper attention has been paid to his diet, a fair store of vitamins, minerals and possibly of protein will serve to tide him over a period of a few days of reduced intake. However, it is not safe to depend on such a margin of safety; it can be depleted rapidly, and insufficient food ingestion may precipitate the child into a condition much more serious than the original illness.

During acute illness, particular attention must be directed to the intake of a readily absorbed and utilized source of energy, together with fluids in amounts sufficient to replace those lost through excretion. If this is not assured, the development of ketosis and dehydration may be expected, either of which in itself may lead to an unfavorable outcome. Fever increases the caloric needs of the body by about 10 per cent for each degree of elevation of temperature. Even in chronic conditions which are not associated with marked elevations of temperature, the energy requirements are considerably higher than would be expected for a child confined to his bed.9 Fuel consumption will not be lessened if food is not ingested; the body's stored foodstuffs or its own tissues will be sacrificed for the purpose. If the patient's condition permits, a diet composed of milk (skimmed, if whole milk is not tolerated), fruit juices reinforced with dextrose, and simple ices will do much to maintain adequate nutrition and to combat the illness. Milk soups may form vehicles for pureed vegetables. Concentrated forms of vitamins A and D may be used at such times with value since the reduced intake of fat may offer less hazard to gastrointestinal upsets. Foods should be chosen with a view to their value to the child, the completeness of the combination offered, their readiness of ingestion and digestibility, and their palatability and attractiveness. While the child's distaste for food may tax the ingenuity of attendants to the utmost, the problem is not met by offering foods merely because they will be caten; the diet should meet the nutritional needs as completely as the situation will permit. It is unnecessary for a patient to lose a considerable amount of weight during a short illness if his attendants are actively concerned with the amounts and nature of the food he receives.

When the nature of the illness or the patient's inability to eat makes it necessary, it is obligatory that nutrient fluids be given parenterally. Ringer's solution is a vehicle of choice since it supplies not only fluid, but also the mineral constituents needed by the body. It can be given by any parenteral route as an isotonic solution; aqueous solutions of dextrose up to a 6 per cent concentration may be added if it is to be given subcutaneously, or in greater concentration if given intravenously. In some situations an aqueous isotonic solution of dextrose (6 per cent) may be fed by gavage to great advantage. When hypertonic solutions are given, they will dilute themselves by imbibition from available body fluids before they are absorbed; for this reason the use of hypertonic solutions of dextrose by gavage, or subcutaneously, is contraindicated. The rate of continuous administration of fluids intravenously should be within the limits of handling by the circulatory system; 3 c.c. per kilogram of body weight per hour is the rate suggested by Marriott, Hartmann, and Senn.10

Diarrhea introduces a serious hazard in the management of acute or chronic illness; it may result in dehydration and may greatly reduce the absorption of ingested foods. Before considering the dietary factors in the management of diarrhea, it is important to emphasize that diarrhea usually must be considered only as a symptom, and may be caused by widely divergent conditions. During acute infectious diseases of any type, the motility of the gastrointestinal tract may be disturbed in such a manner that nausea, vomiting, and diarrhea result. The gastrointestinal symptoms in such patients are not dependent on the diet previously ingested, nor on infection within the digestive Proper therapy will start with a search for the nature and source of the parenteral infection. In the infant and young child this will be found in the upper respiratory tract, throat, or ears in the great majority of instances. When such infection has subsided, either spontaneously or as the result of local treatment, the digestive disturbances will disappear. The dietary management of such patients will not differ from that described in the foregoing. In the case of the infant, acidified feedings may be tolerated better than milk dilutions, and dextrose may be substituted for other forms of carbohydrate with advantage.11 It may be desirable to skim the milk more or less completely or to employ a dilution of evaporated milk. Food refusal, vomiting, and diarrhea frequently result in severe dehydration in infants with severe parenteral infection; to prevent a fatal outcome the use of fluids by some parenteral route frequently is imperative. Marriott and his associates10 advise that in severe diarrhea of any causation the following procedures be employed: restrict all food by mouth;

give by vein an isotonic solution of sodium lactate (Hartmann's solution), reinforced by Ringer's solution and dextrose; slow continuous intravenous administration is preferable, but if the concentrations described above are used, the subcutaneous route may be employed. Transfusions should be used to supplement this form of treatment. When the acute diarrhea has been checked and tissue turgor has been restored, a dietary regimen may be instituted. Milk products, fruit juices and vegetable purées, and an easily assimilable source of vitamins A and D may be used initially, coarser and less easily digestible foods being restored to the diet as convalescence progresses. In diarrheas dependent on bacillary enteritis, as in typhoid fever or bacillary dysentery, the diarrhea is largely independent of the type of diet; adequacy of intake must be maintained in spite of the diarrhea. Readily absorbable foods of low roughage content are called for, well fortified with dextrose or other simple sugar. Because of impaired absorption and the increased energy requirement imposed by the disease, a high calorie intake is demanded. In severe fulminating diarrhea associated with bacillary dysentery, the chief need is for fluids; these patients often die from dehydration, and in spite of vigorous parenteral administration, fluid needs may not be met in sufficient degree to prevent death. Continuous intravenous administration of 5 per cent dextrose solution in Ringer's solution is called for, injected at a rate of 3 to 5 c.c. per minute.

In the treatment of diarrhea in childhood, the use of an apple diet has been popularized during the past few years. In the presence of considerable dehydration, that condition should receive first consideration in the manner outlined previously. In the absence of toxic symptoms, the enteral condition may be treated by feeding nothing other than scraped raw apple, using fruit which is completely ripe and mellow. One to four tablespoonfuls are given every hour or two for a period of forty-eight hours. Aside from water, nothing else is offered by mouth. At the conclusion of the period, the patient is placed on a routine of three meals daily, these consisting of farina. toast, and cocoa made with water, soup with rice, scraped beef with toast, cottage cheese, and ripe banana. After another forty-eight hours has elapsed, boiled milk may be added, then vegetable purée and finally fruit in small amounts. Birnberg,12 in describing this regimen, states that it should not be used for young infants. Minor variants of this procedure are described by various authors. Possibly substances other than apple would be equally effective; Grodecki13 reports that he has used raw ripe tomato for the treatment of diarrhea for thirty-five years, attributing its beneficial effect to its content of vitamins and acids. Fasold has substituted suspensions of cellulose for scraped apple and has obtained satisfactory results; he feels that the action of apple is mechanical and adsorptive. The reviewer has had no experience with the apple cure and does not feel qualified to comment critically concerning it.

Chronic colitis has been attributed by numerous authorities to deficiency of diet. In chronic diarrhea of any origin, impaired absorption predisposes to the development of dietary deficiency. Because of these two interrelated facts, much attention must be devoted to the diet of the patient with chronic diarrhea. The nature of the food residue must be such that it will not lead to additional irritation of

the intestinal mucosa; nutritional essentials of all types must be included in the dietary; and because of the likelihood of wastage through imperfect absorption, the intake of the protective substances must be greater than would be necessary if the intestinal function were normal. Such patients should receive, then, a low residue diet rich in all recognized vitamins and essential minerals, with a liberal protein allowance. The preponderant use of milk and other dairy products, vegetable purées, ripe mellow fruits, fruit juices, meat, liver, eggs. cod liver oil, simple sugars, and limited amounts of thoroughly cooked cereal products should meet the nutritional needs of the patient in a manner compatible with his intestinal condition. In allergic colitis, food sensitivity must be properly treated. Equal attention must be directed to the correction of anemia through transfusions, and possibly the use of vaccines in bacterial forms of the disease. In childhood, such a regimen has led to apparent cure even in proved cases of severe ulcerative colitis.

As a cause or a sequel of chronic inanition, patients may present evidence of inability to absorb ingested foodstuffs in any degree comparable to the normal state. Such a condition sometimes is seen following prolonged misfeeding with foods which are not adapted to the individual's digestive capacity, or following severe debilitating illness. In other patients, the intestinal dysfunction has developed insidiously, without apparent etiology. Chronic intestinal indigestion may vary markedly in degree, and to some extent as to the type of impairment of absorption. Usually these patients fail to absorb fats and complex carbohydrates efficiently, as in so-called celiac disease; sometimes the absorption of fat is less affected than that of starches. The retardation of growth, protuberant abdomen, extreme emaciation, precocious and extreme tooth decay, and the frequent development of rickets and scurvy which these patients manifest offer evidence of the severe nutritional problem that they present. When the usual diet is ingested by such a child, voluminous stools are passed, and marked loss of weight may occur within a few hours. Many clinicians feel satisfied if through their dietary corrections they are able to keep such a child alive and avoid loss of weight, even though normal growth progress is not attained. Yet, through suitable dietary measures, such children have been observed to assimilate an adequate diet, and to resume normal rates of growth.

All patients with absorptive difficulties will utilize protein foods, as a class, better than either fats or carbohydrates. This fact is the basis for the three-phase high protein diet as recommended by Howland, Sauer, Parsons. 15 and others in the dietary management of celiac disease. Sauer states that such dietary treatment has led to rapid and permanent improvement in the majority of twenty-five patients with celiac disease during a period of seven years. The first stage in the diet used by him consisted exclusively of powdered protein milk dissolved in Ringer's solution and given in increasing strength and amount; when the patient's feces gave evidence of good utilization of this food, it was supplemented by the addition of other foods predominantly of protein nature, such as meat serum or scraped lean meat, egg white, or cottage cheese. Powdered skimmed milk may be substituted for the protein milk as food tolerance permits. Under this regimen the body weight should increase, and abdominal disten-

tion should subside. Cod liver oil, orange juice, and iron should also be added to the diet by installments. This phase of the diet control may require continuance for months or years before the patient's food tolerance finally will permit the adoption of the third and most difficult phase of the diet—the introduction of complex carbohydrates in the form of thoroughly cooked starches, and other foods not difficult of digestion. Sauer warns against the introduction of bread, potato, sugar, ice cream, candy, cake, and fresh milk until late in the course of treatment; with recurrence of symptoms, the earlier form of the diet should be resumed. The disease is not cured by this or by the procedures to be described subsequently; dietary control of celiac disease is directed toward the maintenance of nutrition until the lapse of months or years leads to the gradual acquisition of normal digestive tolerance.

While clinical experience has shown that patients with celiac disease can usually tolerate well diets consisting almost exclusively of protein, as described in the foregoing, evidence as to normality of growth and development under such a regimen is not convincing, nor has the necessity for such rigorous limitation been demonstrated. Haas<sup>16</sup> reported the successful maintenance treatment of young children with celiac disease by the use of large amounts of ripe banana: his observations were confirmed by others. The impression was gained that the banana possesses unique properties which account for its tolerance by children with impaired absorptive capacity. Nelson. 17 however, has reported the progress of children with celiac disease under a plan of diet control which provided a liberal allowance of protein in the form of boiled skimmed milk, cottage cheese, egg white, and sieved liver, but which supplied the majority of the calories, as dextrose, orange juice, and tomato juice in large amounts, leading to rapid and permanent gain in weight and subsequently in height. Cod liver oil (1 dram) was given daily. Bananas were used as an acceptable alternative for other types of simple sugars; the sugar of the thoroughly ripe banana is invert sugar, which apparently is well utilized and readily absorbed, whereas more complex sugars may remain in the bowel and undergo fermentation. Metabolic studies indicated excellent retentions of nitrogen, calcium, and phosphorus, and successive clinical studies pointed to good utilization of all the foods mentioned as indicated by the character of the stools and the physical progress of the children. As in all forms of diet therapy in this disease, rigid and continuous adherence to the prescribed regimen was required throughout early childhood; dietary indiscretions always result in copious stools of the type which characterize celiac disease. However, the superior physical progress of these patients and their apparent tolerance for simple sugars indicate that something other than the strictly protein diet is called for in celiac disease.

Because of its ease of assimilability, dextrose is a very valuable adjunct in the feeding of the sick. Stearns and Moore have reported the exceptionally rapid growth and recovery of a three-year-old child with severe mainutrition, which dated from infancy and which was associated with intolerance for complex carbohydrates. He was placed on a dietary regimen similar to that described by Nelson; his food utilization was excellent, as evidenced by his retentions of nitrogen, calcium, and phosphorus, and he gained 11 kg. and grew 14.5 cm. during a period of nine months.

Chronic malnutrition in older children has responded favorably to the same regimen. Stearns, Catherwood, and Kantrow<sup>19</sup> have reported comparative diet studies on five malnourished children, each from 10 to 20 per cent below the average weight for his height. The best and most consistent gain was obtained with a diet of high dextrose content (from 220 to 445 grams a day), high in its content of protein, minerals and vitamins, low in fat and in carbohydrates other than dextrose. More than 45 calories per pound per day were required; good gains were obtained when the value exceeded 50. To achieve similar gains with a diet high in fat and low in dextrose, from 250 to 500 calories more per child per day were required. The protein allowance was about 2 gm. per pound per day. Metabolic studies showed good retentions.

The diets just described are rational; they are composed of foods most readily assimilated, which tax the patient's energies to the least extent; they contain ample amounts of body-building proteins and minerals, and large supplies of vitamins. They can be used successfully for the nutrition of patients with greatly diminished absorptive capacity or of children with normal digestive function. Under the latter circumstances, constipation probably would be troublesome, because of the unnecessary restriction of foods with unabsorbable residue. The inclusion of coarse fruits and vegetables and the substitution of other sugars and starches for dextrose would make the diet suitable for the healthy normal child.

Constipation in children and infants is preponderantly dependent on faults in the diet; correction of the diet will result in relief in all except the small group with organic or functional disturbances which interfere with normal intestinal motility.20 In very young infants, the commonest cause is insufficiency of food; the constinution is only a symptom of the more serious underlying deficiency. Through the use of supplementary or increased amounts of any well-designed milk feeding, normal bowel function may be expected. With the infant of three months or older, who is gaining weight regularly and at a good rate, constipation frequently depends on the absence of sufficient unabsorbed residue in the bowel. Rather than employing even the mildest of laxatives, it is better to add sieved fruits to the daily diet, offering gradually increasing amounts up to an ounce or two daily. The fibrous fruits (prunes, apples, peaches, pears, apricots) are best for this purpose; the sieved pulp is the effective agent, rather than the juice. The dried fruit is stewed and sieved and fed from a spoon. Constipation in the older child may be partly due to habit, but usually it is augmented by the habitual use of diets containing inadequate amounts of the coarser fruits and vegetables. The dietary regimen for a normal child, described in the first part of this presentation. usually will prove anti-constipating; if it is not, it can be supplemented by additional or larger servings of fruits and vegetables. Constipation per se should not be considered as an evidence of illness; it seems to have little or no deleterious effect on the general health.21 It is evidence, however, of the existence of causative conditions, and in the great majority of instances these are purely of dietary origin-

#### THERAPEUTIC DIETETICS IN ALLERGIC DISTURBANCES

Students of allergy have demonstrated the responsible rôle played by tissue hypersensitivity in the causation and modification of many diseases and minor disturbances of physiologic function.22, 24 ubiquity of hypersensitization, the appeal of the new to popular fancy, and the difficulties associated with the establishment or disestablishment of allergy as the principal agent of disease, have led to the attributing of many diverse disease stages to allergy. Let it be recognized that certain conditions obviously depend primarily on tissue sensitization; that in other conditions allergy is one of the important factors in the causation of disease; that in some other conditions the coexistence of allergy may modify the manifestations of a disease dependent on other primary etiologic factors. This recognition makes it necessary to consider the rôle which allergy plays in any given condition, but it should not blind the physician to the need for treating with equal vigor the nonallergic factors contributing to the disease. According to Vaughan.23 allergy must be recognized as a pathologic exaggeration of a normal physiologic response, rather than a pathologic condition per se. Schick24 distinguishes between physiologic degrees of sensitization and the more marked states of hypersensitivity: he would reserve the term allergy for the former and speak of the clinically apparent states of allergy as hyperergy. One must recognize that allergy is responsible for the changes which occur in the body fluids and tissues following specific infections, altering the response of the individual to subsequent exposures to these infections.24 Sensitizations make their appearance following the introduction of many complex substances into the body; they persist for indeterminate periods of time but in general tend to disappear if contact with the sensitizing allergen is avoided.23 While in the majority of instances there is little or no clinical evidence of the allergic reaction in the individual, it may become sufficiently marked to interfere with certain body functions, sometimes to such a degree that the condition is recognized as a state of disease. An individual may be clinically sensitive to numerous allergens in noteworthy degree or may respond only to a few. Because of the prevalence of sensitization22 and the occurrence of marked allergic symptoms in the minority of the population, it is suggested that clinical allergy is dependent on intrinsic as well as extrinsic factors; the individual with pronounced allergy is predisposed through his hereditary make-up to attacks of an allergic nature, and sensitization which will occur as a matter of course in his contacts with his environment will serve to arouse this latent inherent pattern of response. Vaughan<sup>23</sup> states that from 7 to 10 per cent of the population show some outspoken manifestations of allergy; an additional 50 per cent show minor or transitory forms. From a fourth to a half of all individuals will show positive skin tests to various allergens. The list of disease conditions attributed to allergy is long and seems limitless; those with proved relationship are fewer but are of significant number and variety. Evidently certain conditions may have allergy as a contributory cause, yet may exist independently in the absence of demonstrable significant sensitization.

Foods may act as allergens; this is commonest during the first two years of life, and following the fifth year foods are progressively less important as a cause of allergic disease. While the mechanism of sensitization to foods is not clear, it is generally considered to follow the enteral or parenteral introduction of the offending foodstuff or its incompletely digested components. As an explanation for those in-

stances of sensitization of the infant to foodstuffs which he never has been given in his diet. Hill26 believes that they may have reached the fetus following their ingestion by the mother. The usual presence of clinical allergy in some other members of the family is emphasized by most writers on the subject. The foodstuffs most often incriminated in allergy are eggs, milk, and wheat.22 While evidence is not conclusive, there is much to lend support to the opinion that sensitization is dependent solely upon the protein constituents of food and that products which are completely devoid of nitrogenous compounds cannot act directly as allergens.27 An individual may be sensitive to one of the protein constituents of a food but not to others: through certain processing, some proteins may lose in varying degree their property of causing allergy. Ratner and Gruehl<sup>28</sup> have reported studies on the anaphylactogenic properties of milk in which they have compared the response of animals to whole raw milk, milk boiled four hours, canned unevaporated milk, evaporated milk, and dried milk. They state that milk sensitivity is most common to the lactalbumin and lactoglobulin fractions, less so to the casein fraction. ing alters the first two, rendering them less anaphylactogenic. In the unevaporated products, however, the action seems to reverse itself after the milk cools, the products again assuming allergenic qualities. Heat incident to evaporation seems quite effective as a partially denaturizing medium, and individuals sensitive to the whey proteins (milk albumin and globulin) but insensitive to casein may tolerate evaporated milk well, whereas milk in other forms would incite a reaction. Hills states that he has observed sensitivity to egg on numerous occasions where it was certain that the infant had not been exposed to egg since his birth; he attributes the sensitization to prenatal influences and considers the positive skin test as an index of the existence of clinical allergy. The sensitization to cereal products is a function of their protein content, not of the starch; Ratner and Gruehl<sup>27</sup> believe that while various grain products may serve as allergens, they lose this property if they can be purified sufficiently to eliminate the protein fractions. Thus, pure sugars are not allergens and may be used safely in diets of patients with allergy of any nature.

Various methods are employed to determine the foods responsible for allergic reactions in a given patient. Skin tests may be of value, but their evidence is not at all conclusive. The percentage incidence of positive reactors is much greater than those showing clinical evidence of sensitivity<sup>23</sup>; an allergic individual may give positive tests to substances which prove innocuous when tried clinically and fail to react by skin tests to other foods whose allergenic property is readily demonstrable. An individual's food dislikes are not related to his food sensitivities, and no weight should be put on such observations. On the other hand, the patient who is old enough to observe his symptoms in relation to the type of food he has eaten may be able to tell quite accurately that certain foods agree with him while other foods lead to illness. Often allergy to the suspected foods can be demonstrated, according to Vaughan.23 If an accurate diary is made of all foods eaten, the offending foods may be detected through a correlation of the occurrence of allergic manifestations with the previous dietary. When such measures are insufficient, a special diet may be prescribed for diagnostic purposes. Such diets, termed elimination diets, have been described by Vaughan,23 Cobb.25 and Rowe.29,30 They are made up of a minimum number of foods, these chosen from those least frequently concerned with the production of allergy, and with the exclusion of those causing positive skin tests or clinical symptoms in the patient. The resultant diet must be one which at least approximates all the requisites of normal nutrition, since it may be necessary to employ it exclusively for a period of two or three weeks or even longer before forming any conclusion as to the state of allergy. Preliminary to the institution of such a trial diet, Rowe<sup>30</sup> emphasizes the importance of ruling out causes other than allergy for the patient's symp-Hill26 does not attempt to eliminate all foods causing reactions when multiple sensitizations exist, eliminating only those offering greatest evidence of reaction. Because of the uncertainty of composition of commercially prepared foods, none of these can be included in the test diet. Weight maintenance is assured through sufficient ingestion of the sugars, starches, and oils which are specified in the trial diet. Rowe<sup>30</sup> designs his group of elimination diets in such a way that he feels their content of vitamins A, B, C, and G is assuredly sufficient from the amounts of fruits and vegetables included; vitamin D should be included in the form of cod liver oil. halibut liver oil, or viosterol, making sure that the oily vehicle of the latter is one acceptable to the allergic state of the patient. Ultraviolet light may be substituted if circumstances require. He emphasizes that when milk is not offered, the protein content of the diet will be inadequate unless meat, eggs, or legumes are offered two or three times daily; in addition, 4 to 6 gm. of dicalcium phosphate should be given daily when milk is excluded from the diet, in order to maintain sufficient intake of these minerals. In the study of undernourished individuals or children, Rowe<sup>30</sup> offers first a test diet including milk. unless circumstances definitely forbid; suitable milk substitutes such as sobee or cemac may be used under such conditions, or milk may be reintroduced into the diet at the earliest possible moment. As a basic diet for patients with multiple or undetermined sensitivity, he suggests the following test regimen: one or more servings of rice. corn, tapioca, sago, sweet or white potato; one or more servings of lamb, beef, chicken, soy bean, lima bean, dried peas; one or more servings of spinach, carrot, beet, artichoke, asparagus, pea, tomato: one or more servings of lemon, grapefruit, pear, peach, apricot, pineapple. In the preparation of the foregoing, use sufficient amounts of the following: mazola, wesson, olive, or sesame oils; white vinegar if lemon is excluded; salt, cane or beet sugar, and glucose. Quantities of these sufficient to maintain weight should be used. While a whole group of the foregoing may be omitted if necessary, this is not desirable; the test diet must be made metabolically adequate. Rowe29, 20 and Cobb<sup>25</sup> have published elaborately complete menus and recipes, offering series of elimination diets designed to avoid the ingestion of certain individual or groups of foods most commonly found to be allergenic. Vaughan<sup>23</sup> suggests that in eliminating certain foodstuffs, the biochemical or the phylogenetic nature of the suspected foodstuff be kept in mind and related foods be removed as well

Once conclusions have been reached as to the nature and significance of food sensitivity, it is necessary to determine what dietary measures

should be taken. Diets prescribed for continuous use must be constructed with greater care than those used temporarily; since they are diets of exclusion, they also should include enough protective foods and of such a variety that avoidance of any degree of nutritional deficiency is assured. The various published diets for patients with allergy offer varying degrees of nutritional safety; some have been prepared with creditable care from the nutritional standpoint, whereas others appear to have been designed with the allergy in mind more than the welfare of the patient as an individual. It is well to remember that three decades ago, experimental animals were being offered synthetic diets thought complete in essential nutritive factors and that they failed to prosper equally with littermates receiving diets consisting of unrefined foods. While our recognition of nutritional essentials is broader now than then, there is no assurance that it is complete. Growing evidence indicates that better health is assured those receiving diets with generous amounts of protective foodstuffs than those with maintenance allowances. The diet of the allergic individual may easily be restricted to such a degree, through the substitution of biologically sterile energy sources for cruder foodstuffs that likelihood of deficiency disease of greater or lesser magnitude is not improbable.

Some controversy exists between students of allergy diseases as to the relative desirability of desensitization to offending foodstuffs as compared with their continued elimination from the diet. Vaughan23 states that desensitization is unsatisfactory, that avoidance of offenders is better, and that such procedure will lead to a loss of sensitivity to them sooner than will be accomplished by desensitization. With avoidance, sensitivity may be lost within a few months, or a few years, or possibly never; he states that on the average about four and one-half years is required for specific sensitivity to be lost. Ratner,31 in discussing the treatment of milk allergy, advises first the elimination of all whey proteins, rare beef, and beef serum. If the patient has no sensitivity to casein, evaporated milk may be employed during this period if well tolerated. Then a tolerance for unevaporated milk is developed gradually by giving graded amounts daily by mouth, starting out with one drop or even less, and building the daily intake up slowly until in the course of several months the customary amount is being ingested. Once tolerance has been attained, he states that milk must be ingested daily throughout life, to maintain desensitization.

Since specific food sensitivities come and go, it is wise to recheck the patient's state of food sensitivity from time to time, to adapt his diet to his progressive condition, or to restore him to a nonrestricted diet so far as possible.

Dictary Management of Infantile Eczema.—It is easy to eliminate egg and wheat products from the diet of the infant without incurring the risk of qualitative or quantitative nutritional deficiency. Many allergic infants will tolerate evaporated milk when milk ingestion<sup>28</sup> in any other form will result in an exacerbation of the eczema. Ratner<sup>26</sup> found that dried milk preparations, those treated by prolonged boiling, and a commercial milk product advertised as being hypoallergic still retained whey proteins in a form capable of producing allergic reactions in animals sensitized to those types of proteins. When milk of animals of other species is easily available, it may be

tried as a food for the milk-sensitive infant. Hill states, however, that infants sensitive to cow's milk usually react to goat's milk as well. He states that milk sensitivity of infants usually will disappear spontaneously within a few months. The products sobee and cemac-prepared from soy bean and beef, respectively, together with mineral salt mixtures, oils, and other protective substances—have proved of value as milk replacements. Each requires the use of additional foods as sources of energy. Ratner's work<sup>27</sup> indicates that pure crystalline sugars, dextrimaltose, or corn syrup may be used for this purpose, none of these serving as allergens.

The use of concentrated sources of unsaturated fatty acids has been recommended recently as a remedy for infantile eczema, on the premise that there is a deficiency of these acids in such infants.26, 33, 34 While favorable results have been reported by some investigators, others report that no benefit has resulted from their use.35 Linseed oil and corn oil are among the products recommended for this purpose. sitization to the protein of linseed oil has been reported following its

A correlation has been made frequently between the occurrence of eczema in infants and a tendency to obesity. Such infants seem to improve if their weight gain is checked moderately. Urbach<sup>36</sup> states that a reduction in caloric intake together with suitable local treatment frequently will result in healing of the lesions. He recommends feeding the atrophic eczematous infant in a manner to bring the weight up to normal. In the exudative form of the disease, he reduces the intake of fat and of salt.

A review of the literature on allergy and diseases attributed to that condition reveals many contradictory statements, and leads to the impression that much basic physiologic study will be necessary before dogmatic statements can be made concerning the causation, mechanism, and rational treatment of clinical hypersensitivity to protein. In the meantime it seems apparent that any therapeutic approach to these conditions must include attention to nonallergic as well as allergic factors in the etiology and that therapeutic measures which carry the probability of producing a suboptimal state of nutrition should be avoided. Careful planning of the prescribed diet should permit adequate nutrition and yet avoid the use of foodstuffs to which the patient is clinically allergic.

In a subsequent review the discussion of therapeutic dietetics will be continued.

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# American Academy of Pediatrics

## Proceedings

# FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK CITY, JUNE 7, 1935

## Round Table Discussion on the Treatment of Rheumatic Heart Disease in Children

Chairman: Dr. Albert D. Kaiser, Rochester, N. Y. Assistant: Dr. May G. Wilson, New York City.

The meeting was called to order in the Hotel Waldorf Astoria by the chairman, Dr. Kaiser.

CHAIRMAN KAISER.—Rheumatic disease in children is receiving increasing attention on the part of investigators and clinicians. This, I believe, is not due to an increasing incidence of rheumatic infection but to a realization that so little definite information is available on this disease and that it now represents one of the foremost unsolved problems of childhood diseases. Interest in rheumatic infection is not universal, for in certain communities it arouses very little attention on account of its rarity, while in other sections of the country it represents a fair proportion of the physician's contact with pathologic conditions.

Rheumatic infection, especially when the most serious manifestation, rheumatic carditis, is associated with it, is readily recognized as a clinical entity. Some of the factors which are associated with the development of rheumatic heart disease are clearly understood while other factors are unexplained. Because of these unknown factors in the development of rheumatic infection, the specific and effective treatment and control of this disease has not been accomplished.

It seems advisable in this discussion to confine ourselves to some of the debatable matters rather than to review the accepted facts that may be associated with rheumatic heart disease.

The first subject to discuss is to state the problem of rheumatic heart disease in childhood.—Considered from the standpoint of numbers, rheumatic heart disease is not a serious menace to the childhood population. From 1 to 3 per cent of children of school age show chnical evidence of rheumatic heart disease. The seriousness of this disease is shown in the mortality rate of about 13 to 15 per cent during the first five years of the infection. Only a small percentage of those children who survive the five-year period are completely cured. Nearly 50 per cent will have recurrent attacks of rheumatism, and a high percentage will carry their infection into adult life and perhaps die prematurely because of their cardiac involvement. The invalidism associated with rheumatic heart disease may exceed the period associated with tuberculosis in childhood.

The problem of rheumatic heart disease exists among all classes though it is more likely to be found among the poorer classes. It has been stated that in England it is almost entirely an affliction of the poor. In this country such a distribution does not seem to be true. This infection is found in every strata of society in our eastern cities.

It is not likely that rheumitic heart disease is on the increase. Mortality tables show for all ages a steady increase in the number of deaths due to heart disease, but for the childhood period there is actually a decline in the number of children who die from heart disease. This does not mean, however, that the problem is being solved, for the decline in the death rate for this disease is less than the decline noted in any other of the infectious diseases of childhood.

Since the study of heart disease has received such an enormous impetus, the laity as well as the members of the medical profession have become interested in its occurrence. This unusual interest has its unfortunate aspects as well as its useful ones. Children with the slightest complaint referable to the heart and some overhearing discussions on the heart may present themselves as subjects suffering from heart disease. The widespread practice of school health examinations single out many children with so called potential heart disease. When once a child is suspected of having heart disease, it is difficult to distillusion the child and banish the worry that children frequently experience with such an indefinite diagnosis. It is becoming increasingly important for the physician to make a correct diagnosis of heart disease and not call any slight deviation from normal, heart disease. Great harm can be done to the child, especially to the adolescent child, by treating a condition that does not exist.

The question naturally arises: Can rheumatic heart disease always be correctly diagnosed and, if so, what criteria should be utilized?

The problem of diagnosis is encountered chiefly in the milder types of involvement in which the history of previous infection is vague or lacking. Scham has suggested definite means of diagnosis which offer valuable help in separating children with no heart disease from those with heart disease. The following factors, he states, should be carefully investigated:

- I History of rheumatic infection Rheumatic fever Chorca Growing pains
- 2. Fever
- 3. Tachycardia
- 4. Thrill
- 5. Pulmonary congestion
- 6. Circulatory signs
- 7. Weight height index, 10 per cent below
- S. Murmur
- 9. Abnormal roentgen ray observations
- 10. Abnormal esophagographic observations
- 11. Abnormal electrocardiograms

These factors can generally be accurately cheeted. The interpretation of the murmur is likely to cause some uncertainty. To differentiate between functional murmurs and organic murmurs is not a simple matter. The importance of deciding whether a murmur is a functional one or an organic one cannot be underestimated. Interpretation of a functional murmur as an organic one may sentence a child with a normal heart to "cardiac invalidism." Such a child may become introspective and despondent, and oversolicitousness on the part of the parents tends to lead to be havior difficulties. Functional murmurs occur frequently. From 8 to 20 per cent of children have been reported to show functional murmurs at one time or an other. Though many attempts have been made to distinguish a functional murmur from an organic murmur, no satisfactory differentiation has been advanced. In the evaluation of the significance of a murmur, particularly of one heard over the cardiac apex, the decision rests almost entirely with factors other than those relating to the murmur itself. The murmur heard early in the course of an acute rheumatic

infection is frequently soft and blowing and per se may be indistinguishable from a functional murmur. However, the history, together with symptoms and signs of the disease, should serve to differentiate the condition. It is here where the various factors such as x-ray examination and electrocardiogram may be of aid.

The ctiology of rheumatic heart disease is a matter of considerable importance to the physician. The treatment to be instituted may be influenced by the factors that preceded the cardiac involvement. To understand the etiology of heart disease presupposes a knowledge of the causes of rheumatic infection. Unfortunately the causative factors in rheumatic infection are still unknown. Certain related factors, however, are understood, and their recognition guides the therapy. It is anticipated from statistical studies that about 65 per cent of the children with rheumatic fever will develop rheumatic heart disease. In fact it is contended by some investigators that 100 per cent of the children with such a complaint have cardiac involvement. The evidence is not always discernible so that one cannot be sure of the heart involvement. In chorca the incidence of cardiac involvement is somewhat less, about 50 per cent. In the case of children complaining of growing pains or muscular pains the incidence of carditis is about 15 per cent. In approximately 12 per cent of the children studied with undoubted rheumatic heart disease, no previous history of any rheumatic manifestation could be obtained. Much has been written about the significance of tonsillitis and nasopharyngitis as the preceding infection in heart disease. It undoubtedly is the rheumatic manifestation that precedes cardiac involvement in some cases. Efforts to explain a close causal relationship between tonsillitis, rheumatism, and heart disease meet insurmountable difficulties. sillitis is a common infection in approximately 35 per cent of all school children. Yet the incidence of all types of rheumatic infection is less than 8 per cent and less than 2 per cent for theumatic heart disease. In many cases of rheumatic infection no history of tonsillitis or sore throat is obtained. It seems certain that some other unknown factor must be responsible for rheumatic heart disease.

The knowledge that rheumatic disease is most likely to develop between seven and twelve years of age, that it is more prevalent in certain communities such as in the north temperate region, and that it tends to improve or disappear in certain warm localities, is all interesting but has not been of any great help in preventing this infection. The partially understood factors that are supposed to be related to rheumatic infection deserve considerable discussion. Mentioning them may elicit some discussion. Is the hemolytic streptococcus the true etiologic agent in rheumatism? Is a virus associated with this disease? Is it contagious? Is that why it tends to become a familial disease? Is there a family susceptibility to this infection? Does a vitamin deficiency predispose to this disease? Is there a chemical imbalance responsible for the selective action that streptococci display in certain individuals? These queries and others constitute what may be termed the unknown factors in rheumatic heart disease. Investigations under way will soon furnish a reply for some of these questions, but until they are solved all types of rheumatic disease will not be understood.

The treatment of rheumatic disease is a subject for considerable discussion. Inasmuch as the etiologic factors are still an enigma, treatment has been suggested
from various angles. A disease in which pain is usually an outstanding complaint
or in which the nervous and skin manifestations are annoying to the parent demands some form of treatment that will bring relief to the individual. Drug administration has been found most helpful in arthritic conditions. Unfortunately the
relief of symptoms due to drug administration may prevent the patient from getting
the necessary rest which is perhaps of greatest importance in safeguarding the heart.
Though various drugs such as cinchophen and amidopyrine have recently been tried

successfully in the treatment of rheumatic infection, the salicylates in their various preparations still seem to be generally used. The administration of drugs has usually been restricted to initial attacks of rheumatic infection and at the time of recurrences while in the interim no therapy has been employed. A number of studies conducted recently suggests that the prolonged use of an antirheumatic drug may be of benefit in preventing recurrent attacks of certain rheumatic manifestations.

The artificial production of heat, first tried in the treatment of chorea, is now being applied to individuals with rheumatic fever and rheumatic heart disease. It is generally admitted that the symptoms of chorea may be promptly relieved by the intravenous injection of typhoid vaccine or by producing pyrexia in heat chambers. Its application to other forms of rheumatic disease is not well known and deserves discussion.

For awhile the use of vaccines in the treatment of this disorder promised to be of some value. It appears that recent studies nullified some of the advantages first reported. Undoubtedly the method of treatment deserves further study. Based on the assumption that rheumatic children have some constitutional susceptibility which may be due to some chemical or vitamin deficiency, dietary changes have been advocated. A possible disturbance of vitamin C utilization has been suggested as a constitutional weakness in the rheumatic child. Increased amounts of vitamin C have therefore been advised. Our own studies on vitamin C have not demonstrated a deficiency of this vitamin in the blood of rheumatic children. This is, however, an important field for research.

The removal of foci of infection received careful attention during the last fifteen years. At times not only was there a cessation of rheumatic symptoms, but the inevitable recurrences failed to appear. These occasional brilliant results raised the hopes of clinicians in the treatment of this condition. However, after a period of time statistical studies revealed the fact that even after the removal of foci of infection recurrences developed and frequently rheumatic carditis ensued. The removal of the tonsils which were usually incriminated in the presence of this disease failed to bring about the desired result. Nevertheless, the clinical experience demands attention to known for of infection even though the statistical evidence of their importance is not convincing.

The geographic distribution of rheumatic disease suggested that certain climatic conditions were unfavorable for the existence of rheumatic infection. Sending children known to have a rheumatic infection to our southern states or to the West Indies has been the means of aiding these children to a greater degree than any other method of treatment. The impracticability of doing this for any considerable number of children makes this form of treatment available only for the well-to-do class. Further investigation as to the reason that tropical chimates benefit rheumatic individuals may some day reveal a way of giving these benefits to children in temperate regions.

In spite of careful treatment and prolonged convalescent care, rheumatic heart disease will frequently develop in children infected with the rheumatic poison. Even more discouraging is the treatment of rheumatic heart disease. Under the most favorable conditions the end results are disappointing. Stroud recently reported on the end results of 307 children who had rheumatic heart disease and found that 40 per cent were either hopelessly disabled or dead at the end of ten years. This state of affairs is a real challenge to scientific medicine. It cannot be stated that no progress is being made in the control of this disease. Attempts at immunization, desensitization to streptococci, recognizing vitamin deficiency in individuals—any of these procedures may reveal a solution to the rheumatic problem. A discussion of the attempts to utilize these procedures will be of interest to this group, and I hope will subsequently be brought out in our general discussion.

DR WILSON .- Treatment of rheumatic fever in children was discussed:

- I. In its relation to current views of its etiology
  - A. Environmental predisposing factors
    - Environmental predisposing factors
      - 1 Housing, food, hygiene, clothing
      - 2. Climate (change of residence, locality, sanatorium)
      - 3. Contact infection
  - B Prevention of infections (the rôle of respiratory infections)
  - C. Removal of foci of infection (tonsils, teeth, sinuses)
  - D. Rôle of salicylates
  - E Vitamin deficiency.
  - F. Serums and vaccines
  - G. Fever therapy
- II Evaluation of therapeutic measures in relation to the natural history of the disease
  - A. Influence of treatment on symptomatology
  - B Influence on course of disease
  - C. Prevention of occurrences and recurrences of the disease

#### SUMMARY OF DISCUSSION

DR. WILSON.—The importance of the various predisposing factors which would tend to lower the general resistance of the rheumatic child is stressed. Although at the present time there is no conclusive evidence that any of these factors are of specific etiologic significance, our efforts should be directed to favor and improve the general health of these children. The reports given here by representatives from various southern localities concerning the relative prevalence of rheumatic fever would indicate that opinion as to the specifice rôle of climate in this disease must be reserved. The various specific and nonspecific scrums and vaccines which have been used have not met with success and are still only of experimental interest. The importance of caution in evaluating the results of therapeutic measures was emphasized. A long period of observation and a comparable and sufficiently large series of control subjects are essential.

DR ALEXANDER MARTIN (New York) stressed the value of the convales cent care of children with rheumatic heart disease. He felt that acute upper respiratory infections were likely to activate the cardiac lesion in these rheumatic children. The importance of watching the sedimentation rate in these children was stated.

DR. ALFRED J SCOTT (Los Angeles) discussed the incidence of rheumatic disease in southern states. Chorea was larely discovered among children in his experience, but rheumatic carditis was not infrequently noted.

It was brought out in the discussion by various physicians living in the southern states that the classical rheumatic manifestations were not common in their localities but that the disease does occur in a milder or modified form.

DR. L T. ROYSTER (CHARLOTTESVILLE, VA.) discussed the effectiveness of the electrocardiograph in directing the prolonged care of the cardiac child. It also is of great value in deciding whether a child has an organic lesion or is suffering from a so called functional heart disturbance.

The rôle of the tonsils in the prevention and treatment of heart disease is not clear. There seemed to be general agreement that tonsillectomy will occasionally bring about a cessation of rheumatic symptoms though statistically there is very little evidence to support this belief. There is, however, good evidence that the mortality among children with rheumatic heart disease is considerably less in those in whom the tonsils have been removed before the rheumatic heart disease is evident or when it has once been established. It appears wise in the present knowledge of this disease to offer the child this possible benefit even though rheumatic manifesta tions are not eradicated.

### REPORT OF BUSINESS MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

The business meeting of Region III was held in St. Louis, Mo., Nov. 19, 1935, with Dr. Henry Helmholz presiding.

The order of business was as follows:

- I. Report of State Chairmen.
  - 1. Dr. Gengenbach, of Colorado.
  - 2. Dr. Blatt, of Illinois.
  - 3. Dr. Winters, of Indiana, reported for Dr. Torian.
  - 4. Dr. Hill, of Iowa.

Comment was raised over the diphtheria immunization plan reported by Dr. Hill. The point was raised by Dr. Blatt that immunization done in Schick-negative infants who have not lost their immunity may change the child to Schick-positive, and that thereafter difficulties are encountered in making the child Schick-negative again.

Dr. Helmholz suggested the matter was of sufficient importance to refer to Academy committee.

The motion was made by Dr. Feldman, was seconded, and was carried.

- 5. Dr. Carson, of Kansas.
- 6. Dr. Martmer, of Michigan.
- 7. Dr. Berger, of Missouri.
- S. Dr. Huenekens, of Minnesota.
- 9. Dr. Moore, of Nebraska.
- 10. Dr. Pray, of North Dakota.

Dr. Pray in his report brought up the question of Academy requirements for admission to membership. He wished to know whether or not part-time pediatricians were eligible. Also he wished to know whether or not it was the policy of the Academy to give him backing in projects undertaken in North Dakota.

Dr. Grulee answered by saying that the Academy requirements differed in different regions. Region II admits no one unless he is doing strictly pediatrics. In Region III part-time pediatricians have been admitted provided that the consent of other Academy members in the state has been secured. Dr. Helmholz commented that the latter was the policy in Region III.

Dr. Grulee assured Dr. Pray that the Academy would support any reasonable project in his state.

- 11. Dr. Ashmun, of Ohio.
- 12. Dr. Zimmerman, of South Dakota, was not present.
- 13. Dr. Schwartz, of Wisconsin.

Dr. Blatt gave report for Committee on Standardization of State Program.

A motion was made by Dr. Harvey, of Pontiac, Mich., was seconded that the report of Dr. Blatt be accepted and that the Committee be continued; the motion was carried.

A motion was made by Dr. Miner and seconded by Dr. Martmer that a vote of thanks be extended to local Academy members in St. Louis for their courtesy during the meeting; the motion was carried.

A motion was made by Dr. Huenekens, of Minneapolis, and seconded by Dr. Martmer that vote of thanks be extended to Southern Medical Association for invitation to meet with them; the motion was carried.

Dr. Helmholz presented resolution of Chicago Pediatric Society resolving to present name of Dr. Isaac Abt for presidency of American Medical Association, and suggested that other Pediatric organizations of the country might submit similar resolutions indorsing Dr. Abt.

The meeting was adjourned at 12:15.

#### Reports of State Chairmen

Dr. F. P. Gengenbach, Colorado State Chairman.—During the year of 1935, the members of the Academy have participated in the activities of the Denver Public Health Council, the Council of State-Wide Health Agencies, and the completion of a state-wide survey of crippled children.

In preparation for the work to be done under the Social Security Act, the State Medical Society has appointed a committee, the chairman of which is a member of the Academy, Dr. J. W. Amesse.

An effort was made during the sessions of the legislature to pass a bill to reorganize the State Board of Health and to form a State Department of Public Welfare. Both efforts failed but a new Executive Secretary of the State Board of Health has been appointed with a year's leave of absence for postgraduate work at Johns Hopkins. During his absence the position will be filled by a substitute furnished by the U. S. Public Health Service, thus assuring much better cooperation than in the past.

Dr. Maurice L. Blatt, Illinois State Chairman.—The activities during the past six months in Illinois consisted of a scientific meeting of the Pediatric Section of the Illinois State Medical Society at their annual meeting on May 21, 1935, at Rockford. In addition, papers on pediatric subjects were presented before other sections of the Illinois State Medical Society at this meeting.

Following the section meeting, there was a meeting of the Academy members present.

It was decided that members of the Academy write a number of papers for the Educational Committee of the Illinois State Medical Society on pediatric subjects for newspaper release. The responsibility for subjects and assignment to members was given to the chairman. The list of such assignments was accompanied by a letter, an excerpt from which follows:

"The House of Delegates concluded that interviews or articles of an educational nature on medical or health subjects, intended for the lay press or lay audiences, should give expression to the consensus of opinion of the medical profession rather than to personal views which may be in conflict therewith and that articles should appear preferably under the auspices of the American Medical Association or one of its component societies or constituent associations.

"... discussions of new discoveries, of proprietary products, and of special notions may well be confined to medical periodicals, which constitute an open forum for determining the actual status of things in dispute."

The same paragraph applies to all papers delivered over the radio.

A questionnaire prepared at Dr. Grulee's suggestion on the state pediatric organization and pediatric medical service was compiled with the aid of a trained social service worker. After consideration the Illinois Academy members voted that no use be made of this questionnaire pending one which it was anticipated Dr. Martha Eliot would send out.

For Illinois, a committee composed of Dr. Arthur Parmelee, Dr. Henry Irish, and myself, members of the American Academy of Pediatrics, revised a book on infant and child care. Each chapter was written by a pediatrician, a member of the Chicago Medical Society, and so far as I know, each one a member of the American Academy of Pediatrics. This will eventually have wide circulation in the state as it will be distributed with a letter from the State Department of Health.

The Department of Public Health of the state, under Dr. Frank Jirka, and the head of the Department of Child Welfare, Dr. Grace Wightman, are entirely in sympathy with the activities of the Academy.

The relationship between the American Academy of Pediatrics and the Illinois State Medical Society has been one of utmost harmony. Its educational committee,

Talks before

Dr. R. R. Ferguson, chairman, with its permanent secretary, Miss Jean McArthur, cooperated whole-heartedly with any suggestion offered by the Academy.

Miss McArthur has rewritten for newspapers and health publications many of the radio and health talks given by members of the Academy—the extent of this work may be visualized by a summary of the work produced during September and October of this year:

Talks on pediatric subjects before lay groups:

By doctors in general practice	17
By pediatricians	15
scientific meetings:	
By doctors in general practice	2

By pediatricians 7
Two clinics for crippled children conducted (Whiteside and Warren counties):
Radio talks on pediatric subjects 20

Releases to newspapers, September, October, to November 9 (these were on pediatric subjects):

Blackhawk Park Nursery School	18
Regular monthly service to papers	40
To papers	409
Total	467

In addition, hundreds of copies of the radio talks made by the Chicago Pediatric Society have been sent to libraries in Illinois. These were broadcast over Station WJJD during 1931 and 1932, and were written by members of this society. In the library, they form the basis for study of subjects connected with pediatrics; they are used by local writers, teachers, and school children.

Dr. Matthew Winters, Indiana State Chairman.—Our plans for the state include first a tuberculosis survey, which we have well under way in one high school in Indianapolis. We are trying this on one school and intend to extend it after we work out our errors. We are awaiting now funds for the x-ray part of this project.

Our main work in the state of Indiana is one of education. We spend a great deal of our time in improving the pediatric set-up at the Indiana University School of Medicine and have tried to make our courses of study correspond to those recommended by the Academy. We also have a postgraduate committee which takes care of speaking engagements before county medical societies throughout the state and which has sponsored several postgraduate assemblies in pediatrics.

I expect, during the coming year, to make contact with the Parent-Teacher organizations and through them carry on an educational campaign the details of which have not been worked out; but in my work here I find the Parent-Teacher organizations very cooperative.

Dr. Lee F. Hill, Iowa State Chairman.—The report from Iowa, as in previous years, is one concerning the activities of the State Committee on Child Health and Protection. This is a standing committee of the Iowa State Medical Society appointed by the president and reporting before the House of Delegates at its annual meeting.

The Committee now consists of seven members—three pediatricians, two obstetricians, and two general practitioners—two new members having been recently added. The enlarged committee considers the problems of maternal welfare as well as those of child welfare.

As I have stated previously the Committee's chief function is to serve as a connecting link between the State Department of Health and the Iowa State Medical Society. It also cooperates with the speaker's bureau of the state society and

with the various lay organizations of the state active in maternal and child health. The chairman of this committee is a member of the council which represents these lay groups. During the last year one or more members of our committee have attended these council meetings and have taken part in the discussions.

The Committee has also interested itself in securing pediatric recognition on the program at the annual meeting of the Iowa State Medical Society.

In the past the Committee has reviewed all of the literature put out by the State Department of Health and has cooperated with it in its program of immunization being carried out in the various counties of the state. The Committee and the State Department of Health are cognizant of the relatively bad position of Iowa regarding the amount of smallpox present in the state, and steps are being taken to relieve this condition.

A plan, which might be called an experimental plan for diphtheria immunization, is being carried out this month in Polk County—the county in which Des Moines is situated. Cases of diphtheria and deaths from it still occur in this area in spite of free immunization being done by the City Health Department for anyone presenting himself or herself for it.

The plan is build on the premises that immunization ought to be done during the latter part of the first year of life; that the actual administration of the preventive agent ought to be done by physicians in their offices; and that they ought to receive a fee for their services. Furthermore, it was recognized that any effective plan for diphtheria eradication must include provision for the immunization program to be carried out year after year.

Out of a total membership of approximately 200 in Polk County Medical Society, 109 physicians agreed to be in their offices from 11 to 12 on each Saturday morning during the month of November, to give one dose of alum-precipitated toxoid to any infant or child presented at this hour. They agreed to do this for a fee of \$1. The participation of the Parent-Teachers' Association was secured, and members of this organization visited the parents of all infants of the desired age group, explaining the plan, and leaving literature. The radio, press, and street-car placards were used. A vial of alum-precipitated toxoid was furnished each participating physician free of charge by the City Health Department.

It is hoped that this plan will educate the general practitioner in the administration of toxoid and the proper age at which it should be given. Also it is hoped parents will be educated to seek it for their children while the children are still in infancy. If these aims are accomplished, an annual campaign can eventually be discontinued.

More recently our committee has been cooperating with the State Health Department in a discussion of Title V of the Social Security Act. A half-day session has already been spent in considering means for the effective disbursement of federal funds under the first part of Title V—which has to do with Maternal and Child Welfare. These funds will be under the control of the State Health Department, but the plan and the personnel and their expenditure must receive the approval of the Children's Bureau in Washington. Furthermore, they must be expended in areas of greatest economic distress and in rural areas.

On November 21, the State Health Department, the Committee on Child Health and Protection, and the Council of the State Medical Society will meet again for a discussion of a plan which will have been drawn up by the Health Department.

The plan will undoubtedly encompass such features as the education of expectant mothers, education of physicians through lectures and addresses, and immunization of infants and children.

Dr. Paul G. Carson, Kansas State Chairman.—The report for Kansas is one of progress. We are continuing our immunization program, speaking to P. T. A.'s

when possible, and we have offered our services to the State Board of Health in connection with this matter of the national program under Dr. Eliot.

Dr. Edgar E. Martmer, Michigan State Chairman.—The work of the Michigan members has been largely along educational lines. We have attempted to promote both the postgraduate teaching and education of the laity.

In our postgraduate teaching, most of our efforts have been concentrated upon the three-day course for general practitioners given by the members of the American Academy of Pediatrics at the Children's Hospital of Michigan in Detroit. Our first course was given last spring and met with much greater success than we had hoped. The daily attendance for the three days was over sixty men from out in the state. We are planning on repeating this course, covering a different group of subjects, next spring. In addition to this, the members of the Academy are cooperating with the postgraduate extension courses given in cooperation with the State Medical Society, the University of Michigan, and Wayne University. Under this plan, a man will cover one subject in the morning, and a second man another subject the same afternoon. These meetings are held once a week for ten weeks; six units are operated throughout the state.

By cooperating with the Detroit Pediatric Society, the Wayne County Medical Society, and the Detroit Department of Health, we have been able to have a weekly program on the Michigan radio network covering pediatric subjects. In one of the larger newspapers, through cooperation with the Detroit Pediatric Society and the Wayne County Medical Society, it has been possible to carry on a series of newspaper articles covering infant and child care. We feel that education of the laity is an important part of that program and make every effort to assist in the ethical presentation of pediatric information in an effort to combat the large amount of misinformation which is constantly being offered to the public.

We have been able to secure the appointment of one of our members to the Radio Committee of the State Society and the Wayne County Medical Society, thus controlling the pediatric information broadcast.

Through cooperation with the pediatric section of the State Society, a committee has been appointed composed of Academy members, who are likewise members of the State Society, to complete a survey of the use of iodized salt, which was begun several years ago. The original committee was responsible for the introduction of iodized salt in Michigan.

Our efforts toward increasing membership have been greatly curtailed because we feel that with few exceptions all of the men in Michigan who are eligible for membership in the Academy have already applied. Those few who have not done so are planning to apply as soon as their financial condition will permit.

Dr. Harry C. Berger, Missouri State Chairman.—We have now a well-organized and active pediatric society including Joplin, Carthage, Springfield, St. Joseph, Topeka, and Kansas City, Kansas.

The meetings are held once each sixty days, when a scientific program follows a dinner, and this in turn is followed by a free, general discussion. There is much interest displayed, and the men come from all of the centers mentioned. Everyone interested in pediatrics is welcome and attends. However, only members of the American Academy are Class A members. Others are Class B or Class C members. It seems well to enlist the support of as wide a representation as possible to boost any project we want to put under way, and many of the men who are competent doctors and practicing pediatrics are still not eligible to membership in the Academy.

We are ready to carry forward any plan sponsored by the Academy and have in mind some plans of our own to inaugurate. We have developed the closest type of cooperation with the Children's Bureau, and through it, of the P.T.A., which gives us a very strong tie to a powerful lay organization.

So much for the western half of the state. From the eastern half we have nothing. It is my firm conviction that because of the geographic location and the wide divergence of local problems, one state chairman to cover both Kansas City and St. Louis will never be successful. It would seem that one man in each place cooperating closely and with frequent conferences would be highly desirable. It would be well to have either two chairman in the state or one chairman and one vice-chairman.

Dr. E. J. Huenckens, Minnesota State Chairman.—When I accepted the position of chairman for Minnesota six months ago, I found we had a very excellent set-up in Minnesota for public health work of all kinds. There were not only efficient infant welfare organizations in the large cities, but the State Bureau for Maternal and Child Care was well manned and was doing an able piece of work. There was unusual cooperation between the extension division of the University of Minnesota, the State Medical Society, and the Minnesota Public Health Association; Dr. E. R. Meyerding serves as part-time secretary of both the State Medical Society and the Public Health Association. Through these three organization, diagnostic clinics are given throughout the state for the laity, and separate clinics and lectures are arranged for the county medical societies.

In view of this situation, I felt that, since these organizations already in the field were adequately performing many of the tasks that the Academy had set for itself, the best thing I could do would be to offer the cooperation of the Academy and myself in doing their work. This offer of cooperation has been gratefully accepted, and we are all working harmoniously together. If separate action by the Academy should later be necessary, it will be undertaken.

Dr. Clyde Moore, Nebraska State Chairman.—The Nebraska State Committee has nothing in particular to report. We are still working through local organizations, such as the School Health Committee.

The various plans for child health and infant welfare sent out from Washington are so indefinite that all we can do is to try to keep in touch with the work suggested for this state. So far we have been unable to get anything more than a promise that we would be represented on the committee which will outline plans.

Most of our activities are in connection with the Nebraska State Pediatric Society which meets monthly in Omaha or Lincoln.

Dr. R. E. Pray, North Dakota State Chairman.—It is best first to introduce the state of North Dakota to give you some idea of the problems we confront. The general population is about 500,000, scattered over many, many square miles. The population of the largest town is about 29,000; there are about ten towns of five to seven thousand. Another doctor and I are the only two in the state practicing pediatrics exclusively, and in order to make this a success, one must of necessity be associated with a clinic or group practice.

The medical societies and the state association have been very lax in their efforts to assist in the development and training in health matters. Now, with the Social Security Bill definitely on its way, the physician will probably be stimulated to have a great deal more representation than in the past. Control of our state health program has been under Dr. Maysil Williams for the past few years, and she has attempted to work with the medical association without apparent success; the county and town political agencies have been in control of the finances back of the program locally. This has resulted in a political control of the health situation, and with the financial condition of the state such as it is, it has been only too easy for these political units to gain the cooperation of one or more physicians locally in the community to the detriment of the others. There has been very little oppor-

tunity here for a peliatrician as such to make any dent in the program or to assist in establishing a cooperation and a program more in keeping with the standard as desired by the Academy.

The improvement in health conditions of the state as kept by the State Health Department conform pietry definitely with the improvements as seen throughout the entire United States. Perhaps the failure of the medical men to establish a program in health, as it concerns infant mortality and maternal death rate, has resulted in the political powers taking this over through the health departments

Any progress which has been made in gathering statistics and advancing the education of the public has been carried on largely through the nurses, supervised by interests outside the profession. The public in this state have now begun to assume that the nurse is in position to diagnose and treat on a par with the medical man, and we can blame no one but ourselves for this situation

The pair that I, as a representative of the Academy in North Dakota, can play is probably that of attempting to organize those men most interested in pediatrics and through this organization establish a set up which will be able to work with the program as it will be established through the Social Security Act. We will, however, need to feel that the American Academy of Pediatrics will not only stand by us in our efforts but will give us frequent information as to the moves best suited for our advancement in carrying out the wishes of the Academy.

Dr. Sterling H Ashmun, Ohio State Chairman, reported the following:

Special meetings held during year, I.

Membership in state, 60

Eligible to membership, approximately 72

Applications now pending, 4

Cooperated with State Society to obtain representatives on committees in State Society.

Appointment by state director of welfare of state chairman to advisory committee or staff director of work in connection with the Social Security Act when and if appropriations are made.

No definite participation in postgraduate courses, except by members as individuals.

Cooperation with section of pediatries in State Medical Society. No separate state group in Ohio.

General attitude of members, excellent, economically alert. State members voted their cooperation with P. T. A. groups, but discourage the idea of free examination at "spring round ups," which are mere inspections and should not be considered examinations.

Public health association to continue education but to refer actual work of immunization to physicians.

One delegate to State Society House of Delegates.

One member on Child Welfare Committee of State Society.

Dr. A. B. Schwartz, Wisconsin State Chairman.—The uncertainties of the past year in the field of economics have had the happy effect of putting our local medical organizations on their toes. The Academy membership though small has tried to lend direction to these activities of already alert county and state medical so creties.

We have in the main tried to perform an educational function. This has taken three directions

First, the education of the pediatric group in the allied fields of child welfare. As an example, we replaced a clinical meeting of our local pediatric society with a demonstration program at which the workers of one of our local social agencies were the performers

Second, an educational program for general practitioners. This is being done by a regular instruction on some phase of preventive medicine printed monthly on a card and mailed to every member of a county medical society. These are prepared by the Child Welfare Committee of the Milwaukee County Medical Society. (Academy members represent half the membership of this committee.)

Third, an educational program of the public, by directly and indirectly, through the county medical society and other agencies, promoting the idea that preventive medicine is both our tradition and present day concern. As illustrating this phase of interest, we are now in the process of making a survey of available care for the defective child.

Regarding the Social Security Act, the State Medical Society in cooperation with the State Board of Health has already appointed a Committee on Child Health and Protection, which will draw up the program for the maternity and child welfare activities as soon as the funds are made available. A tentative program for these activities has already been considered.

#### Report of the Committee on Standardization of State Programs

At the Rochester meeting of Region III on Oct. 4, 1934, Chairman H. F. Helmholz appointed a committee on this subject.

Members of the committee are Dr. B. W. Carey, Detroit, Mich.; Dr. Lee F. Hill, Des Moines, Ia.; Dr. Oscar Torian, Indianapolis, Ind.

The following program was compiled and sent to each member of the committee. Comments were that the program in general was satisfactory, but that each state should take advantage of what it had already organized.

MAURICE L. BLATT, Chairman.

### Outline of the Program for Region III of the American Academy of Pediatrics (M. L. Blatt, M.D.)

The object of this program is to:

- 1. Elevate the plane of health of infants and children in the region.
- 2. Increase the general practitioner's knowledge of the prevention and cure of disease in childhood.
- 3. Enhance the dignity of that branch of the profession which devotes its efforts to pediatrics as a specialty.
- 4. Assume leadership in all problems concerning the prevention and cure of diseases of childhood and in all public and private organizations having to do with the welfare of infants and children.
- 5. Take advantage of the Social Security Act—Title V, Parts 1, 2, and 3. To assume leadership in carrying out the provisions of this act: (a) by coordinating the activities of the state departments of health; state medical societies; departments of public welfare; Parent-Teachers' Association; Visiting Nurses' Association; social service agencies interested in maternal and child welfare; state hospital associations; state dental associations; state druggist associations; the American Legion; state departments of education; organized private charities; organized re ligious charities; the Masonic groups, and the Elks.

In order to accomplish the purpose of this program, the following agencies should be used:

The organized medical societies of states, counties, and cities, medical colleges and dispensaries, Visiting Nurses? Associations, and child welfare organizations.

and dispersality,

a. Lectures and demonstrations by obstetricians on prenatal care and by
pediatricians on all matters pertaining to postnatal care of infants and children.
For this purpose, charts, lantern slides, and moving pictures will be found of great
assistance.

Plan of Instruction: For the general practitioner, a course of consecutive and planned lectures and demonstrations on prenatal and postnatal problems in child-hood, with special emphasis on preventive medicine. These courses should be taken to the practitioner at meetings of the organized medical society in his city, county, or district. Opportunity to present the subject before such meetings should be sought through the state medical society, district councilors, or county presidents.

a. The course of lectures should be so arranged that there will be no repetition to a given group of physicians within a three-year period.

b. The subject should be of practical value to the man practicing medicine in his own community. Advance in technic, the value of which is in dispute, should not be stressed.

Teamwork: This work should be done by teams organized by the state chairmen of the American Academy of Pediatrics. Popular pediatricians should be selected to head each team, and younger men who will be able to carry on in the future should be assigned to it.

One or two subjects should be assigned to a man, so that the program may be constantly in readiness, and when opportunity arises to present it before a medical group, these men will need little time for preparation. Attempt to balance subjects assigned to each team and put the team as a whole on individual programs if possible.

State Medical Society—Section on Pediatrics: It is advisable to form a section on pediatrics in the state medical societies. This section should have, at most, two sessions, one morning and one afternoon. The papers read should be on subjects of interest, not to pediatricians especially, but to the general practitioner in his everyday handling of medical problems. In Illinois, a single half-day session was found adequate in 1934.

Here, as in the county and district, it is better to take the information to the physician than it is to anticipate his coming to a special meeting to obtain information. In a three-ring circus, such as a state medical society meeting, it is usually difficult to get a physician primarily interested in surgery to leave his section for the purpose of acquiring some newer knowledge of pyloric spasm from a pediatric group.

An effort should be made to have a pediatrician in as many sections devoted to the specialties as is possible. The man should be picked because of his familiarity with the particular problems which confront the special section. The subject should be the pediatric phase of a problem pertaining to their specialty.

State, County, and City Departments of Health: For the purpose of creating a feeling of mutual confidence between pediatricians and the various departments of health, the cooperation of this group of physicians should be obtained. Personal contact, invitation to be present at meetings, and public acknowledgment of their constituted authority are conducive to close harmony of action.

It should be understood that their function is gathering statistics, dissemination of epidemologic knowledge, prevention of the spread of contagious diseases, examination of food and water supply, institution of campaigns in preventive medicine, and the supplying of many biologicals. It should be understood also that the direct contact with the family and family groups is the problem of the physician engaged in private practice, and this should be jealously guarded.

Specific Program: A. Prenatal Care: In order to reduce infant mortality at birth, a wide dissemination of the knowledge of the value of prenatal care is essential. Through the joint effort of obstetricians and pediatricians, use of the press, radio, and public speaking to medical and lay groups, under the auspices of the state medical society, this propaganda may be spread. Papers on this subject should

be read year after year before the general meetings in the county and state medical societies:

The subjects to be stressed are:

The treatment of syphilis in the mother.

Hygiene of pregnancy

- 1. Adequate rest for the expectant mother
- 2. Prevention and cure of vaginal infection
- 3. Care of breast and nipples
- 4. Vitamins during pregnancy
- 5. Adequate diet during pregnancy
- 6. Constipation and hemorrhoids
- 7. Coitus during pregnancy

Danger signs in pregnancy: (a) to mother and (b) to baby.

The value of the pelvimeter.

First signs of labor.

B. Care of the newborn:

Housing, clothing, bathing, feeding, general hygiene, prevention of morbidity and mortality, prevention of infection, care of skin, etc.

C. The child under one year:

Development, feeding, clothing, housing, general hygiene, habit formation, prevention of contagion, prevention of morbidity and mortality.

D. The preschool child:

Organized play, preventive inoculation, diet, habit formation, general hygiene, instruction, discipline, prevention of morbidity and mortality, congenital defects and their treatment.

E. The school child:

Organized play, habits, education, discipline, diet, hygiene, sex education, general survey for physical defects, general survey for tuberculosis, recheck of immunity to preventable contagious diseases.

F. Adolescence:

The psychologic problems, mental hygiene, social adjustment, discipline, organized athletics, selection of future business or profession, prevention of morbidity and mortality.

It will be noted that the above program contains nothing referring to cure of disease. The treatment of disease should not be broadcast to the lay public. It leads to erroneous diagnosis and brings discredit on the medical profession.

The subject of treatment should be stressed in groups made up largely of general practitioners. Nothing sustains their interest so much as specific treatment of disease.

### REPORT OF BUSINESS MEETING OF REGION II OF THE AMERICAN ACADEMY OF PEDIATRICS

The business meeting of Region II was held in St. Louis, Mo., Nov. 19, 1935, with Dr. E. C. Mitchell presiding. Sixty-seven members attended, and all the state chairmen from the fourteen states were present for the first time since the organization of the Region.

A brief review of the progress of the Academy in this region during the past year was given by the regional chairman. It was requested particularly that ap plucations for membership be made out properly at least six weeks prior to the meetings of the Executive Board in November and June.

Prior to the meeting a letter was sent to each state chairman asking that his report embody the answers to the following questions:

- "What new activities have been initiated in your state?
- "How are the old activities progressing?
- "Are you having any difficulties?
- "How are the other child health organizations functioning?
- "Are they coordinating with the Academy?
- "Do you feel that some of the child health activities in your state are not productive of good results?
- "Is your program so constituted that it gives the various members of the Academy some activity to hold their interest?
  - "What children's hospitals have you in your state?
- "Have you any that have been recognized for residency by the Committee on Hospitals as recently published in the JOURNAL?
- "Are you satisfied with the pediatric records now in force in your hospital?"

  Each state chairman gave a complete report. After the reading of the reports and a full discussion, the following matters were considered under the head of new business:
- 1. It was moved and seconded that it is the sense of the majority of our members that there should be some form of certificate of membership issued. All members voted in affirmative.
- 2. It was moved and seconded that the membership of the Academy in this region be restricted to men limiting their work to pediatrics. All members voted in affirmative.
- 3. It was moved and seconded that there should be an associate membership similar to the one formerly in vogue for men interested in, but not limiting their work to, pediatrics. After much discussion, the motion was tabled.
- 1. A motion was made and seconded that a committee of one member from each state investigate hospitals and hospital records, in their respective states and report next year. This motion was carried, and Dr. Wilburt C. Davison, Durham. N. C., was made chairman of the committee; he was to appoint the membership.
- 5. It was moved and seconded that a committee be appointed to draft resolutions on the death of Dr Morgan Smith, Little Rock, Ark. This motion carried, and Dr. A. C. Kirly, Little Rock, and Dr. Ralph Bowen, Oklahoma City, were appointed to draft such resolutions.
- 6. It was moved and seconded that a resolution be adopted thanking the Southern Medical Association for its assistance in making the joint meeting of Regions II and III of the American Academy possible, also for the publicity given to this meeting by the Southern Medical Association. The motion was passed unanimously, and the chairman of Region II was designated to notify the secretary of the Southern Medical Association, Dr. C. P. Loranz.
- 7. A resolution was received from the Chicago Pediatric Society relative to the endorsement by the membership of the Academy as individuals of Dr. Isaac

A. Abt as the next president of the American Medical Association. This was received with enthusiasm.

Chairman Mitchell.—It is very gratifying to find all the state chairmen present for the first time since the organization of Region II. Each state chairman has reported definite progress. The reports would seem to indicate that while in the main the difficulties encountered are quite similar for all states in Region II, each state has a little different problem to meet. By coming together as we have today we can do more toward coordinating our work. Every year we have seen definite improvement.

Some of our chief difficulties come from antagonism from the local state medical societies and from the local health authorities. These difficulties will be entirely ironed out when there is better understanding. The motive of the Academy should be similar to that of the Rotary Club, "Service Before Self." When we can demonstrate to the older and more established organizations that the Academy is organized for the purpose of furthering child welfare, educating better pediatricians, assisting in any educational movement in pediatric education of the profession in general, that the motives of the Academy are entirely altruistic, that we as members of the Academy are willing to act as members of all committees and organizations already established, much of the prejudice will be eliminated.

Several years ago the members of Region II of the Academy and the health commissioners of all states and most of the large cities of the South had a very enthusiastic meeting. Many plans were instituted which did not materialize after the enthusiasm died down, but I still feel that the meeting was productive of good as it gave the health authorities an insight as to the purpose of the Academy; as a result there has been mutual cooperation in Region II.

I should like to comment further that any state in this Region having a good child health program is accomplishing satisfactory results regardless of whether this program is under the Academy auspices.

The American Board of Pediatrics has but one aim—the certification of physicians specializing in pediatrics. This certificate is based on the training and professional attainment of the applicant. The members of the American Board of Pediatrics were appointed jointly from the Pediatric Section of the American Medical Association, the American Pediatric Society, and the American Academy of Pediatrics. The American Academy of Pediatrics is no more an integral part nor has any more voice in the conduct of the Board than have the other two societies mentioned. The expenses incurred by the Board are entirely separate and in no way dependent on the revenue from the Academy. The only connection is that after July 1, 1937, a certificate by the Board will be required of all applicants to the Academy.

As to the opinion that the state chairmen should be elected by the state membership instead of being appointed by the national officers, I believe this could be easily granted. The state chairmen were appointed first from the charter members at the organization of the Society. Many of them still hold that office. In the event of a change the new chairman has been recommended by the regional chairman and the regional board. Speaking as regional chairman, I would be only too delighted to be governed by the members of the state in making this recommendation.

I have always felt that the success of Region II depends entirely upon the organization in each state and upon the industry and ability of the state chairman to control his individual state. As this finishes my four-year term, I wish in closing to thank the state chairmen and the members of this Region for their hearty coperation and to assure them it has been a pleasure to serve to the best of my ability.

#### Reports of State Chairmen

.1labama — State chairman, Dr. Clifford L Lamar; members of the Academy, 11; pediatricians limiting their work, 23

All of the Academy members in Alabama with the exception of two live in Birmingham, and so far we have not attempted any organized activity. We are not aware of any work to be done at the present time without financial backing far beyond our means. What we have attempted to do was to acquaint the various agencies who re ceived children with the fact that we are here, and both able and willing to serve. About a year ago we called a meeting in Birmingham of the Department of Public Welfare, the Transient Bureau, and the Red Cross and told them who we were and what we could offer them The meeting was successful as far as it went. The other agencies represented knew us through our representation as individual members on When the map showing infant mortality was sent out by Dr. Eliot, I immediately went to Montgomery to the State Department of Health with it and asked them to locate the responsibility. They checked over their reports and said that the chief difficulty appeared to be in the obstetrical field, a statement which I felt lifted the opprobrium from our specialty. When the federal government sug gested the possibility of aid in the state health work the Department of Health called a meeting in Montgomery of all of its workers to acquaint them with the prob This meeting was held last summer and a committee from the Academy at tended and offered its services. Six of the "refresher courses" in pediatries were given in Alabama during the summer months The State Medical Association shared the expense with the Children's Bureau. We feel that the Academy has too few members to attempt any activity as an association and that we can serve best as a reference bureau for the various agencies who have child health problems.

Arkansas—State chairman, Dr. A C Kirby; members of the American Academy, 4; pediatricians limiting their work, 5

The first active work was initiated last April at the meeting of the State Medical Society when Dr. Morgan Smith, then state chairman, organized the State Pediatric Society. This society admits all members of the State Society in good standing who are interested in pediatrics. There were 46 present at this meeting. Dr. Morgan Smith was elected president; Dr. A. C Kirby, vice president; and Dr. Madeline Melson, secretary treasurer. Unfortunately, Dr. Morgan Smith died this last year. There were no further activities until there was a second meeting in Little Rock, November 1, attended by members of the Academy in the state, and Dr. C. G. Grulec, secretary, and Dr E C Mitchell, regional chairman, of the Academy. It was decided at this time to have a program given under the auspices of the State Medical Society and the State Pediatric Society beginning April 28, 1936. The program will be as follows: three papers of one hour each in the morning—the first on immunity and contagion; the second on diseases and accidents of the newborn; and the third on tuberculosis in childhood These pipers are to be followed by a luncheon with round table conferences at which the three essayists will lead the discussion. Speak ers are to be announced later. At the same time there will be a business meeting of the State Pediatric Society to determine a program to be presented for the ap proval of the State Medical Society and the State Health Department.

Florida — State chairman, Dr. W. W. Quillian; members of the Academy, 10; pediatricians limiting their work, 18.

Florida reports the first meeting of the newly organized State Pediatric Society (membership open to all members of the State Society interested in pediatrics) will be held concurrently with the annual meeting of the State Medical Association in May, 1936. Practically all eligible pediatricians in the state are interested in the regional program and are enthusiastic. Difficulty has been encountered in coordinating efforts for child health activities on account of the widespread geographic distribu-

tion of the Academy members. The policy has been to encourage local activities in the larger cities of the state under the supervision of the pediatricians in these In Tampa Dr. George Cook, with the assistance of Dr. Martin and Dr. James Cowart, has arranged a program for the year. In Jacksonville Dr. Luther Holloway and Dr. Thomas Buckman are attempting lay education toward periodic physical examinations of the well child, and have arranged flying squadrons of teams consisting of recognized pediatricians, obstetricians, and public health officials who have addressed various mothers' clubs and Parent-Teacher organizations. At Miami effort is being made by the Academy group to provide a place for the proper training of the backward and mentally deficient child. The Dade County Parent-Teacher Association is assisting in an effort to obtain diphtheria immunization for all preschool children. Education of the medical group has been attempted through the medium of the extension course given under the auspices of the State Medical Association at Gainesville in June. Dr. Horton Casparis delivered a series of lectures and informal discussions during a week of varied activities. Preventive pediatrics was stressed. Attendance consisted of physicians from the entire state, and an average of two hundred were present at this meeting. A permanent committee for the study of maternal and infant mortality has been selected from the State Medical Association. No funds are available for a study of this problem from the viewpoint of the pediatrician. It has been felt that more can be accomplished at present by assistance to existing agencies for the improvement of child health than by organization of independent groups without proper financial backing to accomplish an extensive program. The pediatricians of this state are accomplishing a great deal in education of laymen to the value of preventive care and the consequent improvement of child health. The majority of Academy members in Florida feel that membership should be composed of competent men who are limiting their work to pediatrics, and that some form of certification should be granted in recognition of this membership.

Georgia.—State chairman, Dr. M. Hines Roberts; members of the Academy, 16; pediatricians limiting their work, 38.

Georgia has the most complete and satisfactory program, through the organization of County Councils and Child Health and Welfare Councils, of any state in this region. This state also has a very active State Pediatric Society which presented the following program in December, 1935:

#### AFTERNOON SESSION-

The Medicinal Fish Oils-Dr. Charles E. Bills, director, Research Laboratory Mead Johnson Co., Evansville, Ind.

The Thymus Delusions-Dr. John Lovett Morse, Emeritus Professor of Pediatrics, Harvard University Medical School, Boston, Mass.

The Progress of Infant Feeding—Dr. Isaac A. Abt, Professor of Pediatrics, Northwestern University Medical School, Chicago, Ill.

#### EVENING SESSION-

Address of Welcome—Dr. Edgar D. Shanks, president of Fulton County Medical Society

Response to Address of Welcome—Dr. Mercer Blanchard, President-Elect of the Georgia Pediatric Society

Infection, Immunity, and Vaccination in Acute Anterior Poliomyelitis-

Dr. John A. Kolmer, Professor of Medicine, Temple University, Philadelphia, Pa. Introduction by Dr. Geo. F. Klugh, Jr.

Diagnosis and Prognosis in Pediatrics-Dr. John Lovett Morse

The Multiple Nature of Vitamin D.-Dr. Charles E. Bills

A Child's Heart in Avitaminosis-Dr. Isaac A. Abt

As the Georgia report has already been published in the JOURNAL no further presentation will be made at this time,

Kentucky.—State chairman, Dr. Philip F. Barbour; members of the Academy, 10; pediatricians limiting their work, 13.

The Kentucky members of the Academy have been quite active during the past year. We hold a postgraduate course each spring, one day a week for ten weeks, for general practitioners who are within driving distance of Louisville. The lectures and demonstrations of all kinds are held in the Children's Free Hospital, giving the doctors an apportunity of seeing the new hospital methods of treatment. At our request the Children's Free Hospital also allows any doctor in the state to spend a day or week in the hospital wards without charge. We are also having teams of two pediatricians go out through the state to make contacts with the various women's organizations, to make health talks before the luncheon clubs, and to hold clinics and round table conferences with doctors in the district. These have been very favorably commented upon wherever the teams have visited. We are planning for many more of these the coming year. In addition, of course, there are many of the various county societies before which members of the Academy have presented papers. These more formal affairs do not seem to have been as successful as the other type of talks. I have been in quite close contact with our able secretary of the State Board of Health, Dr. McCormack, in formulating plans for the Social Security set-up. These are now showing definite shape, and when the General Assembly has approved the plan, the various members of the Academy will be used as much as possible in this work. There are a good many men in the state who report themselves as doing pediatric work, and we are trying as far as possible to affiliate with them. However, nearly every man who limits himself to pediatrics is a member of the American Academy of Pediatrics.

Louisiana.—State chairman, Dr. Robert A. Strong; members of the Academy, 18; pediatricians limiting their work, 28.

Louisiana has an active Pediatric Society composed of all members of the State Medical Society interested in pediatrics, as well as pediatricians, which has been in existence for several years.

As no report has been received from the state chairman the activities of the Academy in this state cannot be given in detail.

Mississippi.—State chairman, Dr. N. C. Womack; members of the Academy, 6; pediatricians limiting their work, 10.

The State Pediatric Society of Mississippi held a called meeting on November 6, 1935, at which the executive officer of the State Board of Health was present. After a general discussion of the best methods of promoting child welfare in Mississippi, the following resolutions were adopted:

- 1. The Mississippi State Pediatric Society and the Mississippi State Board of Health will seek the approval and cooperation of the Mississippi State Medical Association in putting on a two-year program in maternal and child welfare, conducted by a pediatrician of outstanding ability. This program is to be put on in every county in the state, similar to the one now being conducted in obstetrics under the supervision of the State Board of Health. A committee from the State Pediatric Society was appointed to cooperate in developing this program.
- 2. In cooperation with the State Board of Health and under the control of the State Board of Health, the same groups will work for the development of the county-unit plan, which is at present in operation in Washington County, and which is operated principally through the local Parent-Teacher's Association. This is a year-to-year campaign with a definite program of prenatal, natal, and postnatal education of the mother; immunizing all preschool children against infectious diseases, general lectures on child health, nutrition, etc.

The State Pediatric Society, through their individual members, are cooperating in every way in their local communities to promote the cause of child welfare in all its phases.

North Carolina -State chairman, Dr. Aldert S. Root; members of the Academy, 18; pediatricians limiting their work, 30.

On June 27, 1935, Dr. George M. Cooper, director of the maternal and infant welfare work of the State Board of Health, acting as special agent of the United States Children's Bureau, called a meeting of certain pediatricians, obstetricians, and general practitioners in order to discuss a maternal, prenatal, infant, and child health program, which was to be submitted to Dr. Martha Eliot for approval, in order that North Carolina might obtain its quota of funds from the Daughton Bill.

After a general discussion of the subject a committee of four was appointed to submit a definite plan to Dr. Eliot for her consideration. this committee, Dr. T. L. Lee, Dr. Bayard Carter, Dr. H. H. Johnson, and Dr. A. S. Root, outlined a plan as follows:

A Plan for the Reduction of Maternal and Infant Mortality in North Carolina

- 1 The employing of a full time competent obstetrician and pediatrician.

  The duties of these men shall be:
  - a To conduct postgraduate courses in obstetrics and pediatrics for physicians
  - b The obstetrician to instruct midwives in caring for normal cases and to recognize gross abnormalities
  - c. In conjunction with local health departments to supervise prenatal and infant welfare clinics
  - d To conduct public meetings on maternal and infant welfare
- 2 The local county medical society must approve the plan and pledge its support before any activity is started in that particular county.
- 3 All prenatal and infant welfare clinics to be organized by local county medical societies in conjunction with local county health departments. All physicians in county to be invited and urged to take part in these clinics. The obstetrician and pediatrician employed by the State Board of Health to act in an advisory capacity only. The clinical material in these clinics to be utilized for postgraduate in struction as said obstetrician or pediatrician may see fit.
- 4 The employing of public health nurses trained in social service work where these clinics and postgraduate courses are organized. The duties of these nurses shall be to instruct mothers, to get them to the clinics, to follow up the cases, and to disseminate information concerning maternal and infant care.
- 5 The obstetrician and pediatrician employed by the State Board of Health shall report their activities each month to the committee.
- 6 As soon as the plan is in operation, an extensive publicity campaign on maternal and infant welfare is to be put on. This to include both newspaper articles and radio programs prepared by the State Board of Health and the obstetricians and pediatricians of the state.
- 7 An effort shall be made to set aside a small sum of money for necessary diugs, sundries, etc., to carry on this work
- 8. Realizing that to reduce materially the high maternal and infant mortality in this state some means must be provided for early hospitalization of complicated cases, the State Board of Health, this committee, and the president of the North Carolina Medical Society will make every effort to make funds available to carry out this section of this plan for the reduction of maternal and infant mortality in North Carolina. If and when these funds are available for hospitalization, the patient is to be intimidated in no way by anyone connected with the administra

When funds are available and the actual work begins, the members of the American Academy of Pediatrics in the state will share the work of carrying it out

Ollahoma -State chairman, Dr. Clark H Hall; members of the Academy, 14; pediatricians limiting their work, 16.

Since July 1, the new health commissioner of Oklahoma has instituted children's clinics over the state. These are general, including physical examinations and immunization. His force is limited, but he hopes to add to this with an increased grant of funds The Oklahoma Society for Crippled Children, a state organization, is doing excellent work. During the year of 1934 there were nineteen clinics held in various cities over the state with a total of 717 children examined. Many of these children were referred to hospitals for treatment. The expenses of the society are paid by a state appropriation and membership fees. A full time secretary is em ployed. By state law, the commission is authorized to cooperate with the federal authorities and to do all things necessary to entitle the state to receive the benefit of such provisions as Congress may enact for such purposes. The Academy has not had a specific program this year. Every member is cooperating in carrying on the following work. The last legislature passed a law whereby any child whose parents cannot afford medical treatment can be sent to a hospital at the expense of his county. These hospitals must be approved by an appointed committee nine hospitals in the state that have been approved as capable of handling such cases. Each staff man who is to take part in this work must be approved by the committee. He must devote at least a major portion of his time to this specialty The proper papers are filled out and sent to the county judge. He then sends the child to one of the approved hospitals for hospitalization. The hospitals receive a certain sum per day. There is one strictly Children's Hospital in the state, the Hospital for Crippled Children, which is operated as a part of the University of Oklahoma Hospital and Medical School It has a capacity of 200 beds, and the convalescent home has a capacity of 50 beds. The hospital is general, but a large portion of the beds are designated for orthopedies. The resident spends six months in this hospital and six months on medicine in the general hospital. It is approved by the American Medical Association as such. Our members have expressed the opinion that there should be some form of certification. It is our opinion that the membership of the Academy should be composed of men who limit their work to pediatries entirely. If not, then the Academy would cease to be of as great value to the men limiting their work. We are not in favor of a classification for anyone other than pediatricians The State Pediatric Society should take care of all those with a major interest in the specialty.

South Carolina -- State chairman, Dr. D. Lesesne Smith; members of the Academy, 5, pediatricians limiting their work, 15

South Carolina has an active Pediatric Society, the membership composed of men limiting their work to pediatrics, though it is my understanding that the meetings are open to all members of the State Society who are interested in this branch

The Academy group in South Carolina has been quite active, but owing to the fact that up to the present time no report has been received from this state we are unable to report activities in detail

Tennessee -State churman, Dr. Horton R. Cisparis, members of the Academy, 23; pediatricians limiting their work, 36.

Tennessee has an active Pediatric Society, which has been in existence for four years. The membership is composed of all men in good standing in the State Medical Society who are interested in pediatrics. A program, which is essentially practical and very interesting, is given each year for the general practitioner as well as the specialist. This year in Memphis there will be a clinical feature added. At luncheon there will be a session of the American Academy to which all members of the State Pediatric Society are invited and where there will be a discussion of the various child health problems.

A position of director of child health for the State Department of Health has been created and will function in the very near future. The various child health organizations of the state are attempting to coordinate their activities under the super-

vision of the members of the State Pediatric Society. The local health departments in the large cities, particularly Memphis, have been quite active, owing to the high infant mortality rate reported by the Bureau of Census A recent survey was made by Dr. Ella Oppenheimer of the Department of Child Welfare under the Department of Labor. This survey was quite complete A thorough analysis was made, and many health suggestions emanated from this report. These suggestions have been taken into consideration by the local health department and will be carried out. We hope to report more progress within the next year.

Teras - State chairman, Dr. Edwin G Schwarz, members of the Academy, 36; pediatricians limiting their work, 72

Letters have been written to all members of the Academy in Texas, encouraging them to carry preventive pediatrics and child health information to the various medical societies It has been suggested that the pediatric departments of the Uni versity of Texas and Baylor Medical College foster an educational program. The services of the Academy have been offered to the state health officer and to the president of the Federation of Women's Clubs of Texas, and the services of the Academy members offered for any health program. At the Third Conference of Child Health and Protection the state chairman acted as chairman of the medical Through the secretary of the State Medical Association, together with the state health officer, we have outlined a plan for pediatric instruction throughout the state under the Social Security Act A meeting of the state group was held at the tall meeting of the Texas Pediatric Society, which about twenty members attended and at which we were honored by the presence of Dr. Grulee. At this meeting it was the consensus of opinion that no reduction in membership requirements be made and that the executive committee, through the regional chairmen, supply each member with a report on the anticipated activities to be brought up at the following annual meeting in order that those in attendance be better qualified to act on these new activities

Virginia - State chairman, Dr. J B Stone, members of the Academy, 18, pedi atricians limiting their work, 30

During the past year the Department of Clinical and Medical Education of the Medical Society of Virginia in conjunction with county medical societies has spon sored five postgraduate courses in pediatrics in widely separated parts of the state Three of these were under the leadership of Dr. George M Lyon, Huntington, W. Va, and two were under the leadership of Dr Samuel F. Ravenel, Greenshoro, N. C These courses were well received by the local physicians and considered a success in every way. Both the University of Virginia and the Medical College of Virginia have continued their practice of giving short postgraduate clinics each year. St Phillip Hospital Post Graduate Chinic for practicing colored physicians has been held each summer at the Medical College of Virginia for the past five years Bureau of Child Health of the State Department of Health has been very active m promoting the "Five Point Program" among school children, as a minimum standard of physical fitness Leading up to this, much work has also been done on the "Beginner's Program" in an effort to have all preschool children examined, preferably by their family physician, and remediable defects corrected before enter ing school. This bureau has continued to wage an active campaign against diph theria, and strenuous efforts have been made to increase the number of immuniza fions by family physicians and in clinics The State Department of Education, realizing the need for more and better instruction regarding infant and maternal hygiene, has included a health unit in its revised curriculum. This unit stresses the importance of proper infant care and the necessity for a healthful and sanitary en vironment. Last year a booklet, Health Survey of Virginia's Children, was pre pared and published under the direction of the State Committee of Child Hygiene of the Cooperative Education Association, Virginia Branch of the National Congress of Parents and Teachers. This survey discloses many facts regarding present conditions and should be of tremendous usefulness in making an attack on existing problems. Last April the State Child Conservation Committee was formed, the purpose of which is to coordinate the activities of the various state-wide organizations concerned with the promotion of child health. This committee is composed of the Child Hygiene and Child Welfare Committees of the Medical Society of Virginia, the Virginia Pediatric Society, the Virginia Tuberculosis Association, the Cooperative Education Association, and the State Superintendents' (of schools) Association. At the organization meeting of the group, committees were appointed to make a study of the following subjects, and make recommendations.

- 1. Appropriations for a continuous postgraduate service to Virginia doctors.
- 2. Pro rata appropriations for indigents from state and counties for local hos pitalization for specific needs.
- 3. Pro rata appropriations from state and counties for correction of vision in indigent children with special reference to the use of local specialists.
- 4. Pro rata appropriations from state and counties for correction of teeth in indigent children.
- 5. Pro rata appropriations from state and counties for immunization of indigent children.
- 6 State appropriation for specific drugs furnished physicians for treatment of all cases of venereal disease.
- Appropriations for a tuberculosis control program with especial reference to pneumothorax.

The Academy is well represented on these committees, and some of its members are engaged in furthering the work of the organization.

The Academy as a unit has made very little headway in Virginia. It has been quite difficult to get the members of the Academy together and to have them look on the Academy as their own organization in which they are an integral part; the trend has been for them to expect the Academy to do something for the members instead of their doing something for the Academy.

There has been, among other things, some complaint of the Academy dues. A number of the members seem to identify the Academy with the American Board of Pediatrics and express dissatisfaction with the latter and with the Academy as a part of the Board. Their contention is that membership in the Academy should in itself constitute certification of pediatric competence which should be evidenced by a certificate of membership issued by the Academy. They think that the fee for certification by the American Board of Pediatrics is unjust and that this should be covered by the dues paid to the Academy.

The opinion has also been expressed that the state chairman should be elected by the state members instead of being appointed by the National Officers, and they look on this appointment as an infringement on local self-government.

The Pediatric Society has been somewhat loosely organized in the past, and its meetings held at a brief luncheon period once a year have not given adequate time for matters that should be considered. But at its meeting in October a partial reorganization was effected, and it was decided to hold an additional all day clinical meeting each spring. It was agreed that a short period of time would be set aside at this spring meeting each year for discussion of Academy activities.

West Virginia -State chairman, Dr. J. Lewis Blanton; members of Academy, 9; pediatricians limiting their work, 19.

One year ago the West Virginia Pediatric Society, a section of the West Virginia Medical Society, was called in special session by members of the Academy to formulate plans for a state child welfare program. A summary of the proposals approved at this meeting was presented to the West Virginia Medical Society at its annual meeting in May of last year. This led to the appointment by the State Medical

Society of a child welfare committee and a maternal welfare committee. committees have been active during recent months developing plans for a state program of child and maternal welfare. Full cooperation with existing health and welfare agencies has been maintained. So far, the program has consisted in laying the foundation for future efforts and stressing the educational side of child and maternal welfare through various means of publicity. A program of postgraduate education for the rural practitioners of the state is being developed for the coming year. These committees are also working out the details for a state program for child and maternal welfare under the provisions of the Social Security Act. Individual members of the Academy have been quite active in their respective communities. Dr. George M. Lyon has developed a school health program for Cabell County, which is ie ceiving favorable comment from many national organizations interested in child well Dr. Holland and Dr. Blanton have given a series of health talks over the radio on preventive pediatrics. These talks have been given under the auspices of the Marion County Medical Society and have stressed particularly early immunizations. Dr. Andrew Amick is chairman of our State Child Welfare Committee. Dr. Russell Bond, Dr. A. A. Shawkey, and Dr. Raymond Sloan are Academy members on this same committee. West Virginia, because of the large mining population, presents many difficult problems for the committees on child and maternal welfare, but we feel confident that these problems can be solved and that much good will come out of the program now being evolved.

West Virginia suffered a real loss when Dr. R C. Hood was appointed director of the Crippled Children's Division of the Children's Bureau in Washington, Dr. Hood was one of the most energetic pediatricians in the state. His interest in the pediatric activities of our state, and his wise counsel, will be greatly missed. However, the pediatricians of the nation can be assured that the Crippled Children's Division under the Social Security Act will be well administered.

### Academy News

Dr D. B. Leitch, of Edmonton, has accepted the chairmanship for the Province of Alberta.

Dr. Howard Spohn, of Vancouver, has accepted the chairmanship for the Province of British Columbia.

Information has just been received that Dr. Cail K. Wagener, of Pittsburgh, died Feb. 26, 1935.

The next annual meeting of the Academy will be held at Kansas City, Mo., on May 11 and 12 preceeding the meeting of the American Medical Association. Head quarters for the Academy Meeting will be the President Hotel

### News and Notes

The Fourth International Congress of Pediatrics, which was scheduled for this spring in Rome, has been postponed until the latter part of September, 1936.

### Book Review

Mechanics of Normal and Pathological Locomotion in Man. ARTHER STEINDIFE, M.D., F.A.C.S. Professor of Orthopedic Surgery, the State University of Iowa. Iowa City. Iowa Charles C. Thomas, Springfield, Ill, and Baltimore, Md. Price, \$5.00

The author presents a very detailed and well reasoned summation of the normal and pathologic mechanics of the human body. It is primarily intended for the use of those who, as orthopedic surgeons, must treat severe deformities resulting from injuries, congenital anomalies, or advanced pathologic derangements of body mechanics; but it will repay careful study by those who, as pediatricians, need a clearer understanding of the mechanical forces acting within and upon the body as a basis for teaching correct posture and efficient use of the body to normal children. The first group will, no doubt, find it necessary and profitable to understand the extensive mathematical and physical formulas used as proof of the explanations given, but no one should be deterred from careful reading of this book by the simpler process of accepting the author's conclusions with the assumption that his mathematical illustrations are sound. These conclusions are so clearly stated and the illustrations so numerous and well done that they are in themselves a veritable store house of practical knowledge.

For example, one with but a rudimentary knowledge of mathematics and physics can readily understand and be greatly enlightened by Dr. Steindler's description of the process by which the human body, all of whose movements are about articulations and are therefore rotary movements, can transpose these purely rotary movements into translatory motions

"When rotation of a body occurs about a single point fixed in space, for instance in the case of a pendulum or wheel, the result can never be anything but a rotatory movement. Now let us combine two such rotatory movements of a member of the skeletal structure by causing it to rotate alternatingly about both ends. For the sake of illustration we shall take a straight rod and imagine that it turns successively first about one end and then about the other. If the rod is rotated about its lower end, it will swing forward at a certain angle, the same as a swinging pendulum. Let us now imagine that it stops at the end of the swing and that it thereupon proceeds to rotate about its upper end and that it now describes the same are about the upper end while the lower end remains free to swing forward. The result of these two rotatory motions is that the position of the rod at the end of the second rotation is exactly parallel to that of the starting position, but it has been brought forward by a certain distance." (Page 19.)

"So we see that combinations of two or more rotatory motions can be arranged to result either in a translatory progression, if the angles are equal and opposite, or in the summation of the rotatory effect, flexory or extensory, if the angles are not opposite in direction " (Page 21.)

Likewise, his chapter, "The Center of Gravity," is very interesting, instructive, and important interesting because of his use of many types of animals for illustrative purposes and his deductions concerning the philogenetic development of posture in animals and man, instructive because of his emphasis upon the necessary development of the extensory muscles of the back, hips, knees and ankles without which upright bipedal posture cannot be maintained, important because without

an understanding of the effects of the force of gravity on the body such as is given here, no one can teach children to make the best use of their muscles and thereby avoid faults of both equilibrium and motion. The following paragraphs on the relation of equilibrium to motion are classical examples of clear thinking.

"Only when the equalization of forces does not take place and resultant forces become active, a loss of equilibrium occurs under the appearance of motion. Thus, it is proper to define: motion is loss of equilibrium.

"In human locomotion the loss of equilibrium does not mean that the individual falls to the ground. On the contrary, it is part of the scheme of locomotion that loss of equilibrium is promptly followed by another period in which equilibrium is regained to the extent of preventing the fall of the body. That means that the threatened fall is intercepted by new forces which are created by additional muscle action for this specific purpose. Then recovery of equilibrium is again followed by a phase in which it is destroyed. We may therefore define locomotion as a rhythmic play of muscle forces between loss and recovery of equilibrium." (Page 32.)

Space does not permit too detailed a review of this excellent monograph, but I cannot forbear quoting at length from the chapter, "The Spinal Column."

"Why is the human spine not a straight rod but a quadruple curve? The curves are the result of developmental changes the spine has undergone from its early embryonic phase to the state of complete adult formation. In the latter half of embryonal life the spine shows only one single curve with a posterior convexity, the curve reaching from the occiput to the pelvis. This is the configuration of the spine in the newborn. In the adult, however, the spinal column has taken on several curves, alternating with each other in converse direction.

"The first of these curves appearing additionally to the embryonal curve is the lordosis of the cervical spine. It develops as the head is being held erect when the child attempts to enlarge its horizon of vision.

"The second curve develops by lordosing of the lumbar spine when the child begins to sit up and later to stand.

"Between the cervical and the lumbar lordosis the dorsal spine retains to a measure its original convexity and one may speak of the normal kyphosis of the dorsal spine.

"The curve which begins at the junction of the fifth lumbar and the sacrum and which includes sacrum and coccyx, has its convexity backward; it is a kyphotic curve.

"There is a great physiological latitude in relative length and degree of these curves. Yet, each curve is compensatory to its neighbor with the result that the line of gravity, as it passes from the supporting base, intersects with all four curves of the spine at a certain level. Owing to this feature of compensation, the spine finds itself generally in line with the line of gravity, in spite of the fact that each curve in itself marks a deflection in anteroposterior direction. The result is a more or less even distribution of the body weight in front and back of the line of gravity.

"The first function of the spine is to maintain upright posture. Clinically, one may describe normal posture as follows: head erect, the eyes look straight forward, the shoulders are square, the chest is well rounded and is carried forward of the abdomen (Goldthwait). There is full extension of the hips and full extension of the knees. The feet are at right angle position to the leg and the toes point straight forward or slightly outward.

"Mechanically, the definition of normal posture is based upon the already mentioned relation of the spine to the line of gravity. Seen in the frontal plane, it spinous processes of the vertebrae, and intersects with the head at the middle of in two symmetrical halves.

"In signital projection, that is, viewed from the side, the relation of the line of gravity is as follows. It arises from the supporting surface of the feet between ball and heel, in front of the ankle joint, slightly in front of the knee joint, running directly behind the center of the hip joint, ascends between hip joint and sacrum to cut the upper and anterior portion of sacrollac junction; then it runs upward behind the bodies of the lumbar spine, intersects the spine at the lumbo dorsal junction, then runs slightly in front of the dorsal spine, intersects the spine again at the cervice dorsal junction, runs slightly behind the cervical vertebrae, and finally touches the head immediately behind the ear at the mastoid process." (Pages 120 and 121.)

What pediatrician his not been asked by many anxious mothers, "Is my baby's back deformed?" when she first notices the physiologic lordosing of the lumbur spine described here?

The mechanics of the ankle and the foot and of the gait are especially recommended for careful study, and the mechanics of posture for even closer attention

I have long noticed that there is a definite relationship between the excessive lumbar lordosis of the Class C posture and marked or excessive shortening of the posterior leg muscles and that correction of the posture fails or proceeds very slowly unless the posterior leg muscles, especially those of the calt, are subjected to vigor ous and simultaneous stretching. I have also felt certain that these two conditions, ie, the lordosis and posterior leg muscle shortening, react one upon the other to form a vicious cycle in progressively bad posture. While I have been certain of this relationship and have used it as a clinical fact with excellent results, it was not until I read Dr. Steindler's explanation, which leads up to his sentence (Page 197). "As soon as the line of gravity wanders in front of the ankle joint, which is the case in the usual normal position, then the calf muscles come under tension; on the other hand, when the center of gravity wanders back of the knee joint, tension 18 produced in the extensors of the knee," that I clearly understood the mechanics of this fundamental relationship. Likewise, while I have taught, with all my powers, that the military posture is abnormal and should not be used as the "correct" posture, as it is by nearly all directors of physical education, I did not have the firm foundation for my convictions which his excellent explanation has given me, nor did I realize the usefulness of the military posture for its one purpose, namely, that from this position "a sudden forward movement of the body can best be under tal en "

"The so called military posture is also an incidental upright posture. The thorax is maintained vertically and carried forward; the abdomen is drawn in and the pelvic inclination is increased. The knees are extended. The common center of gravity of the body is thrown in front of the ankle joint and in front of the knee joint, so that tension of the calf muscles and relaxation of the knee extensors occurs. Lumbar lordoms is accentuated. (Reviewer's italies.)

"Because in this position the center of gravity of the supia femoral mass of the body is considerably in front of the common axis of the hip joint, the extensors of this articulation are under considerable tension. This tension still increases if the weight of a rifle held in front of the body further transposes the line of gravity forward. This is not a rest posture by any means; it is a posture of attention out of which, due to the tension of the glutcals and calf muscles, a sudden forward movement of the body can best be undertaken." (Pages 197 and 198.)

If these two paragraphs alone could be instilled into the minds of all educators, this book would take a high place in the literature on this subject, and would save millions of children from the misconceptions which are now contributing to the continuation of, and in all too many individuals, an actual exaggeration of an already faulty posture.

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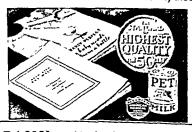
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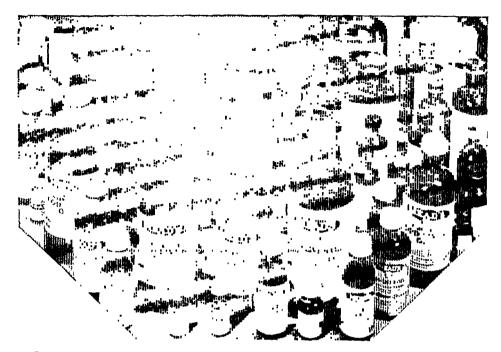
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